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# College of Physicians
## *of*
# Philadelphia

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TRANSACTIONS & STUDIES

*of the*

College of Physicians of Philadelphia

Volume 14
(Fourth Series)

Number 1
(April 1946)

# Leukopenia: Its Classification, Etiology and Treatment*

*By* JOHN S. LAWRENCE, M.D.

LEUKOPENIA occurs in a variety of conditions. Its significance varies depending upon: first, the disease or the condition which is responsible for it; second, the presence or absence of granulocytopenia; and third, the degree of the leukopenia. For example, little significance is attached to its presence in undulant and/or typhoid fever. In these conditions the degree of leukopenia is not great and there is no appreciable granulocytopenia. On the other hand, a very serious import is associated with its presence in sulfonamide therapy, particularly when the granulocytes disappear.

An attempt will be made in this discussion to classify leukopenia and then to discuss in some detail some of its clinical manifestations and the therapeutic procedures used in combatting it.

It should be understood at the outset that leukopenia usually represents only one part of the general clinical picture. The proper evaluation and therapy of it involves an insight into the general disorder with which it is associated. Frequently, it is of minor significance as compared with other abnormalities which are present. For example, the leukopenia in primary anemia and/or sprue is only an incidental finding. Also, in aplastic anemia the thrombopenia and the anemia frequently cause more disturbance than the leukopenia. Hence, while this discussion is limited to leukopenia, it must be recognized that the interrelationship of leukopenia with other abnormalities is presupposed in all instances.

In order to have any clear concept of leukopenia, one must have some classification of it. I am not familiar with any completely satisfactory classification of leukopenia. In 1941 (1), I advanced the following physiological classification:

1. Leukopenia due to diminished manufacture of white blood cells. This may be the result of (a) simple inhibition, (b) maturation arrest, (c) aplasia of the bone marrow, and, (d) infiltration of the bone marrow with foreign cells.

2. Leukopenia due to increased elimination of the white blood cells: (a) loss of cells through infected areas; (b) elimination of cells in amounts greater than normal through usual channels.

3. Leukopenia due to increased rate of destruction in the peripheral blood due either to abnormal white blood cells or to abnormal substances in the blood channels which cause destruction of the white blood cells.

4. Redistribution of the white blood cells in the vascular channels, such as occurs with foreign proteins.

5. Redistribution of the white blood cells in the body as a whole, as seen at times in leukopenic phases of leukemia.

While this classification is of some value in consideration of the mechanisms responsible for

* From the Medical Department of the University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and the Rochester Municipal Hospitals. Delivered before the Section on General Medicine of the College of Physicians of Philadelphia, March 25, 1946.

leukopenia, it is not a satisfactory clinical classification. Accordingly, I would like to present the adjacent clinical classification:

*Clinical Classification of Leukopenia*

| I. | II. | III. | IV. | V. | VI. | VII. |
|---|---|---|---|---|---|---|
| L. accompanying acute infectious diseases | Idiopathic L. | Toxic L. | L. associated with intrinsic medullary disease | L. associated with splenomegaly and/or hepatomegaly | Nutritional L. | Hoarding L. |
| 1. Bacterial — e.g. typhoid fever, hrucellosis, some overwhelming infections<br>2. Viral—e.g. influenza, epidemic hepatitis, "atypical" pneumonia, measles, and roseola infantum<br>3. Protozoal — e.g. malaria and kala-azar<br>4. Platyhelminthic —e.g. chronic schistosomiasis | 1. Acute<br>2. Chronic<br>3. Recurrent and/or cyclic | 1. Acute l. due to<br>(a) drugs — e.g. amido-pyrine, sulfonamides, thiouracil, gold compounds, arsenicals and other drugs<br>(h) radioactivity<br>2. Chronic l. due to<br>(a) drugs<br>(h) radioactivity | 1. True aplastic anemia<br>2. Pseudo-aplastic anemia<br>3. Myelophthisic anemia<br>(a) Carcinoma with metastases to the bone marrow (rarely)<br>(h) Leukemia, leukopenic type or phase<br>(c) Hodgkin's disease (rarely)<br>(d) Lymphosarcoma (rarely)<br>(e) Myelosclerosis (occasionally) | 1. Cirrhosis of the liver<br>2. Chronic congestive splenomegaly<br>3. Idiopathic splenomegalies with leukopenia<br>4. Gaucher's disease<br>5. Massive derangement of the spleen as with tuberculosis or syphilis (at times)<br>6. Felty's syndrome<br>7. Certain hemolytic anemias (at times)<br>8. Agnogenic myeloid metaplasia of the spleen (at times) | 1. Folic Acid deficiency<br>(a) Pernicious anemia<br>(b) Sprue and Idiopathic steatorrhea<br>(c) Other clinical types of folic acid deficiency not recognized at present<br>2. Malnutrition<br>3. Lupus erythematosus disseminata?<br>4. Hypochromic anemia, chronic, of long standing | 1. Anaphylaxis—foreign protein reactions |

It is readily admitted that this classification has many weak points. However, it can be used, at least, as a means of getting together the various clinical types of leukopenia.

The physiological mechanism involved in leukopenia associated with acute infectious diseases is not, in all instances, known. Thus the leukopenia in typhoid fever may be due to: (1) increased destruction and/or elimination of white blood cells; (2) diminished manufacture of white blood cells; or (3) a combination of (1) and (2). I suspect increased destruction is the most important factor since there is a distinct increase in the number of early polymorphonuclear neutrophiles. Boyd (2), however, explains the leukopenia by the changes in the bone marrow. I have made no detailed studies of the leukopenia in bacterial infections. However, studies have been made in this laboratory (3) on one type of viral leukopenia—viz., that due to infectious feline agranulocytosis. This is an infectious disease occurring spontaneously in cats. It is characterized by marked leukopenia and neutropenia without anemia. It is due to a filterable virus. Inclusion bodies have been demonstrated in the reticular cells of the lymphoid tissue, in the epithelial cells of the gastro-intestinal mucosa and in the alveolar epithelium of the bronchial mucous glands. Marked reduction in the myeloid elements of the bone marrow and absence of differentiation of the myeloid cells such as is seen in agranulocytosis due to drugs in the human occur at the height of the disease. Thus, in this disease the leukopenia is due, at least in part, to changes in the bone marrow. This does not, of course, prove that changes of this nature are responsible for leukopenia in other viral infections. In fact, we know that comparable changes cannot be found in many instances. However, even though morphological changes are not present there may be functional derangements. I have made no detailed studies of the bone marrow at the height of leukopenia in influenza, epidemic hepatitis and similar conditions. Lucké (4) has

reported moderately hyperplastic marrow in infectious hepatitis.

My experience with protozoal infections is so limited that no comments are indicated.

Idiopathic leukopenia has been used to include certain unusual instances of leukopenia of unknown origin. Acute, chronic and recurrent and/or cyclical types occur. In the period between 1930 and 1935 a good many instances of the acute type were seen. Many of these patients probably had leukopenia due to amidopyrine.

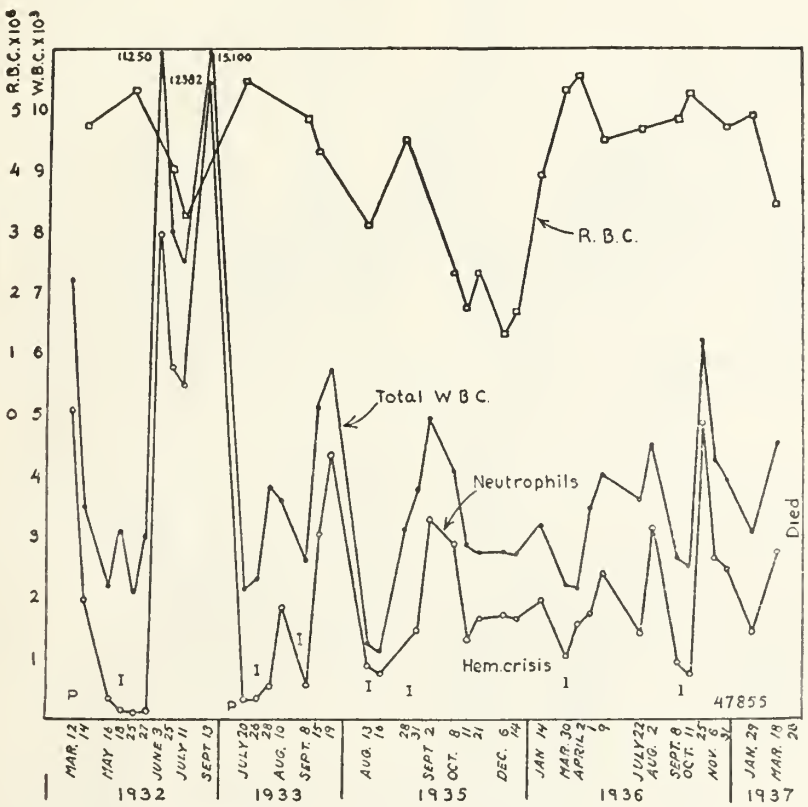


CHART 1. Chronic idiopathic leukopenia. I—infection. P—amidopyrine. Hem. crisis—hemolytic crisis.

Chart 1 gives the salient blood findings in a male, unit number 47855, 18 years of age, who had chronic idiopathic leukopenia. This young male was followed in the Strong Memorial and Rochester Municipal Hospital Clinics over a period of five years. His first admission was in 1932. At that time he gave a history of repeated epistaxes for one and one-half years. He had thrombopenia at the time of his first admission but he had no further trouble of any note with abnormal bleeding even though he did have recurrent thrombopenia throughout the period of observation. His course was characterized by *repeated infections* up to the time of his death in 1937. As indicated on the chart by the letter I, he had infections usually when his neutrophiles reached a low level. Some of the infections which he had were epiglottiditis, perichondritis of the larynx, cellulitis of the mouth, the buccal mucous membrane, the gums and the right mandible, noma of the right cheek and osteomyelitis of the right mandible. This young male did not develop splenomegaly. He was given pyramidon on at least two occasions while in the hospital as we did not, at that time, appreciate the significance of this drug with reference to agranulocytosis. However, this drug probably had nothing to do with his blood picture as it persisted after this drug was interdicted.

The recurrent or cyclical type of idiopathic agranulocytosis is illustrated in chart 2. These findings were reported by Stephens and Lawrence (5) in 1935. The patient was a 38 year old widow who was observed in repeated attacks of agranu-

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locytosis. These attacks coincided with her menstrual periods but continued to recur regularly after bilateral oophorectomy for a period of one year. At that time, she ceased taking all drugs, after which she had only one more period of neutropenia. She is living and engaged in active work at the present time. Her blood findings have remained normal during this interval.

locyctosis due to sulfonamides, thiouracil, gold and amidopyrine. It is important to recognize that leukopenia and/or agranulocytosis due to drugs differ depending upon the drug responsible for the condition. Thus it has been shown repeatedly that agranulocytosis due to pyramidon is a hypersensitivity reaction as indicated in the original reports of Madison and Squier (6)

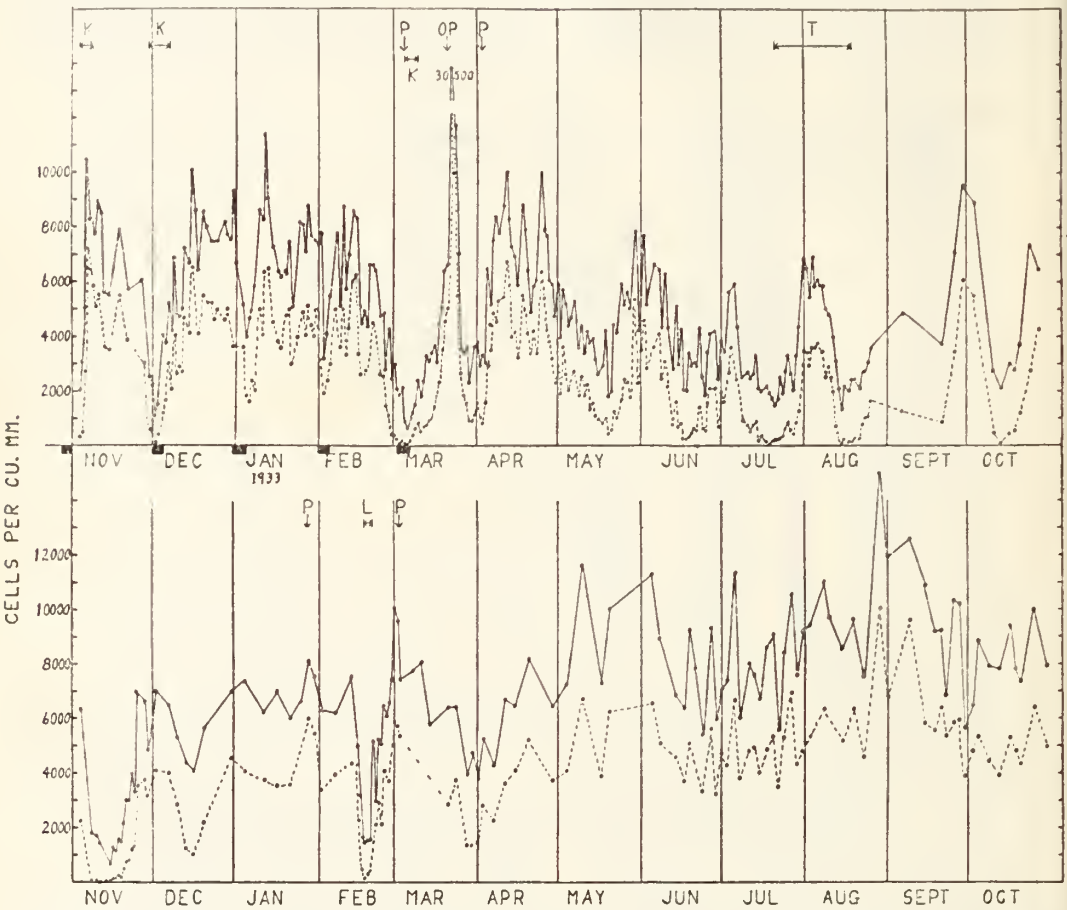


CHART 2. Recurrent or cyclical agranulocytosis. Solid line: total leukocytes. Broken line: neutrophiles. The areas blocked in black represent the menstrual periods. K—pentnucleotide K-96, 20 c.c. daily intramuscularly. P-amidopyrine, 5 grains by mouth. OP—bilateral salpingo-oophorectomy. T—theelin. L—Lederle's parenteral liver extract, 6 c.c. daily intramuscularly. Stephens, D. J. and Lawrence, John S.: Annals Int. Med., **9**: 31, 1935. (Courtesy of *Annals of Internal Medicine.*)

Cyclical cases of this type are rare but have been reported from time to time.

Toxic leukopenia includes a group of conditions familiar to most clinicians. Drugs of various sorts, radioactive substances and, rarely, overwhelming infections by organisms usually causing leukocytosis are responsible for this type of leukopenia. All of you are familiar with acute agranu-

Squier and Madison (7), and Watkins (8) in 1933 and 1934. On the other hand, no hypersensitivity usually develops in those patients who develop agranulocytosis as a result of the sulfonamides. In these individuals, the drug may be given in most instances after recovery without the development of agranulocytosis a second time. Furthermore, agranulocytosis does not usually

develop from these drugs until rather large quantities have been given. Finally, the mortality is much lower in sulfonamide than in pyramidon agranulocytosis.

Thiouracil seems to be more like pyramidon in respect to hypersensitivity. Readministration of the drug following its production of agranulocytosis may be followed by a second episode of agranulocytosis (9, 10 and 11). The recent reports by Moore (9) and Van Winkle and associates (10) are the most comprehensive ones on agranulocytosis and leukopenia due to thiouracil. Moore (9) found the incidence of thiouracil agranulocytosis in 1091 patients treated with this drug to be 1.8 per cent with a mortality in the agranulocytosis cases of 26.0 per cent. Leukopenia without agranulocytosis in this series was 3.0 per cent. Death attributable to the drug was found to be 0.5 per cent. Van Winkle and associates (10) in a survey of 5475 cases found the incidence of agranulocytosis to be 2.5 per cent with a mortality of 14.0 per cent for the agranulocytosis cases. The mortality rate for their entire series was 0.4 per cent. Leukopenia was found to have an incidence of 4.4 per cent. Thus, the incidence of agranulocytosis in thiouracil therapy can be assumed to be approximately 2.0 per cent and that of leukopenia approximately 4.0 per cent. There is one significant difference in these two reports as regards the period when agranulocytosis has its highest incidence. Thus, Moore (9) found the period between the fourth and the eighth weeks of treatment to be the most likely one for agranulocytosis to develop whereas Van Winkle and associates (10) found that more than one-half of their cases of agranulocytosis occurred during the first month of treatment. There is general agreement, however, as to the occurrence of most of the reactions of this sort during the first eight weeks of treatment. Van Winkle and associates (10) state further that administration of the drug in cases in which leukopenia without agranulocytosis has developed results in "a gradual return of the white cell count to normal limits" in nearly one-half of these cases. It would seem from these reports that sensitivity is present in thiouracil agranulocytosis but that it is not as constant as in pyramidon agranulocytosis. Further the mortality rate does not seem to be as high in thiouracil as in pyramidon agranulocytosis.

We have had in the clinic of the Strong Memorial and Rochester Municipal Hospitals, 19 patients with agranulocytosis presumptively due to pyramidon. Of these, fourteen died and five recovered. On the other hand, six patients with sulfonamide agranulocytosis recovered and there were no deaths due to agranulocytosis of this type. One patient with thiouracil agranulocytosis recovered. His main findings are shown in chart 3. He was a 64 year old male who had a toxic nodular goitre, unit number 225835. Thiouracil was given in a dosage of 0/6 gram daily for 10 days and then in a dosage of 0/4 gram daily for the next 12 days. The total white blood cell level did not reach an extremely low value due to the large numbers of monocytes which appeared in the peripheral blood. No treatment was used other than discontinuation of the drug. A small lesion appeared in the mouth at the end of the agranulocytic period but rapidly disappeared.

Few comments are necessary with reference to leukopenia due to intrinsic medullary disease. It is obvious that the number of the cells may be diminished materially if the bone marrow is aplastic or markedly deranged. It should be pointed out that leukopenia is not a constant finding in myelophthisic anemia. In fact, it is more common to get leukocytosis with a shift to the left due to what we call an irritative reaction. However, leukopenia may occur.

I have no explanation for the leukopenia that occurs in association with splenomegaly and/or hepatomegaly unless it is due to increased destruction by the reticulo-endothelial cells as advocated by Doan and Wright (12). This seems the best explanation for the leukopenia which Wiseman and Doan (13) have designated primary splenic neutropenia as the leukopenia is entirely relieved by splenectomy. The leukopenia of chronic congestive splenomegaly is relieved by splenectomy also. This is not true in all leukopenias associated with splenomegaly and/or hepatomegaly, however.

Charts 4 and 5 give the principal hematological findings in two patients who had leukopenia associated with splenomegaly. The patient whose findings are given in chart 4, was a male, unit number 31519, 45 years of age at the time of his first admission to the Strong Memorial Hospital. At that time he had had persistent bleeding from the nose and gums associated with thrombopenia, for two weeks. He had splenomegaly and hepatomegaly. Throughout the six year period of observation he had recurrent infections and bleeding from various areas. He was given many transfusions. Reference to the chart shows that

he usually had infection when the number of his neutrophiles dropped appreciably.

The patient whose findings are given in chart 5 is a most unusual one. She, unit number 12084, was 50 years of age when first seen in our clinic in 1928. At that time she had an upper respiratory infection and marked leukopenia. She has been seen at repeated intervals since then and has run a persistent leukopenia. In 1939 she developed thrombopenia and hemorrhagic tendencies for which she had a splenectomy in 1944. The results were very satisfactory. She has had no further bleeding. She had a temporary post operative leukocytosis with a return to leukopenia. Blood studies on February 25, 1946 revealed a white blood cell count of 5750 per cu. mm. with 44 per cent of neutrophiles. These figures are the highest she has had at any time during the entire period of observation except immediately after splenectomy. The remarkable thing about this woman is the absence of repeated infections throughout this prolonged period of leukopenia. Whether she is going to maintain a normal level of white blood cells now, cannot be said. Splenectomy *may* have had a beneficial effect on the leukopenia as well as the thrombopenia.

Nutritional leukopenia is well known and is assumed to be due to diminished manufacture of white blood cells as a result of the absence or diminution of some essential substance. All of us are familiar with the return to normal of the white blood cell picture in primary anemia as a result of administration of the erythrocyte maturation factor. Recently, following the successful synthesis of folic acid in the Lederle and Calco Chemical Division Laboratories (14) and a large amount of experimental work dealing with the effect on the blood of vitamin B deficient diets by many investigators, several reports have been

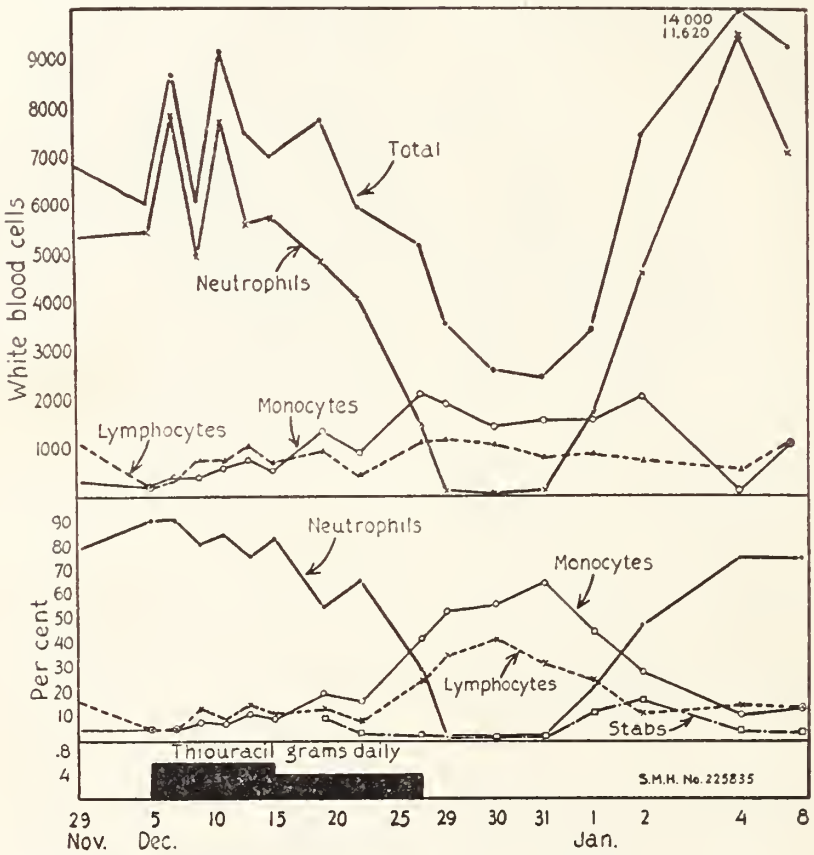


CHART 3. Agranulocytosis due to thiouracil

made on the successful treatment of primary anemia and sprue by folic acid. The leukopenia associated with these conditions has been combatted as well as the other abnormalities. These results establish the fact that folic acid deficiency may produce leukopenia in the human as well as in the monkey and the rat. It remains to be seen how many other types of leukopenia in the human may be corrected by folic acid.

Hoarding leukopenia is not of much clinical significance as it is usually of short duration. It is frequently seen following the injection of foreign proteins, e.g. typhoid vaccine.

The fact that the neutrophiles may disappear from the peripheral blood within a few hours after the administration of amidopyrine to a patient hypersensitive to this drug, led Fitz-Hugh (15) to postulate that peripheral destruction was probably a factor in these cases. In 1941 I (1) made a report in which I accepted this possibility as a partial explanation for the sudden disappearance of the neutrophiles in cats with infectious feline agranulocytosis. However, observations in this laboratory since then have made me retract this. Recently we have published observations (16 and 17) which seem to us to indicate pretty clearly that the white blood cells do not remain in the peripheral blood a long while. Our results indicate that the white blood cells of the cat are replaced about one and one-half times in 24 hours.

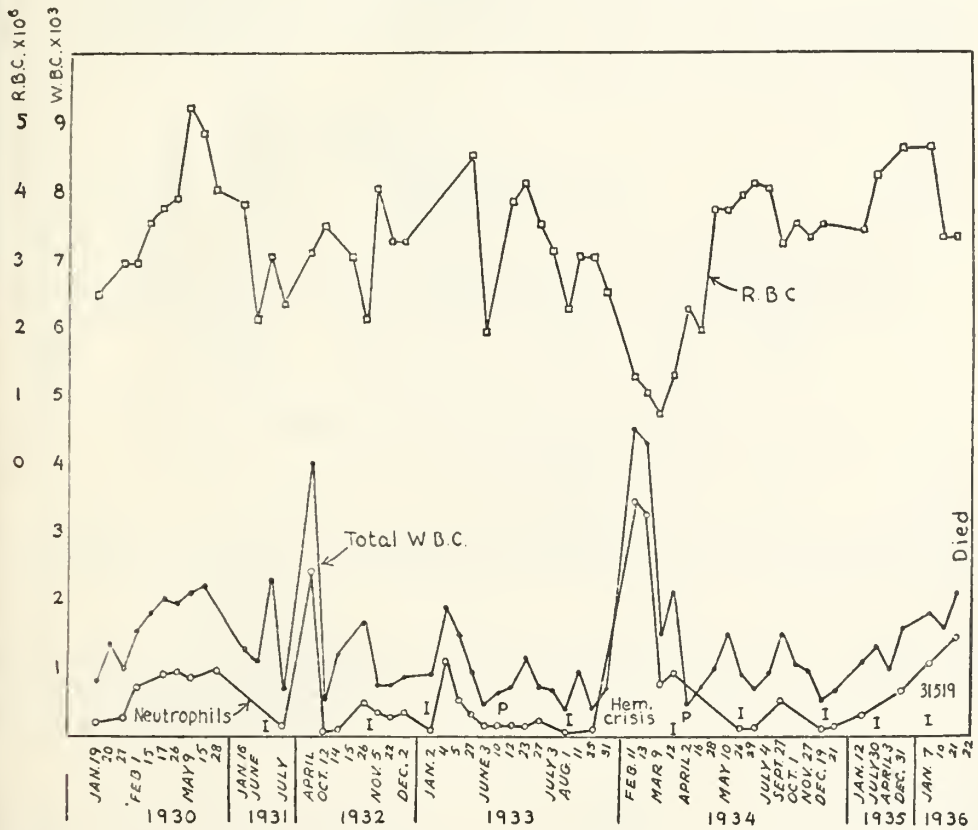


Chart 4. Leukopenia associated with splenomegaly. I—infection. P—amidopyrine. Hem. Crisis—hemolytic crisis.

Charts 6 and 7 and tables 1 and 2 give evidence in support of this statement. Charts 6 and 7 and table 1 give results previously reported (16) on the rate of disappearance of white blood cells in leukopenic animals. In these experiments animals made leukopenic by irradiation had their level of white blood cells increased by cross circulation with normal cats. Then, the animals were disconnected and the rate of disappearance of the white blood cells determined. From table

CHART 5. Leukopenia associated with splenomegaly

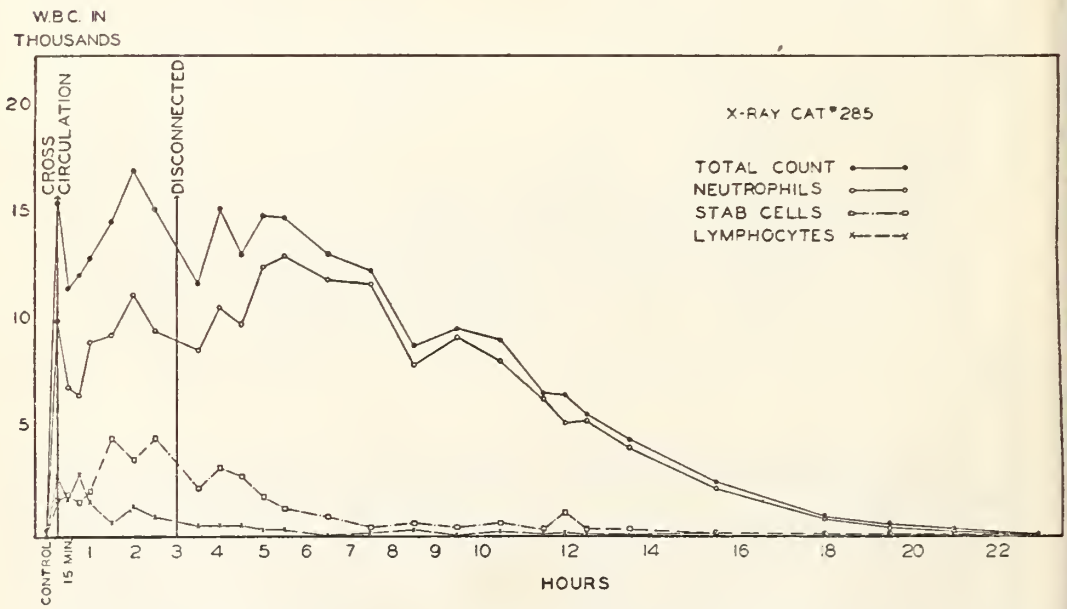


CHART 6. This chart shows the changes in the white blood cell picture of a leukopenic irradiated cat during and following a period of cross circulation with a normal cat. Lawrence, John S., Ervin, Donald M. and Wetrich, Raymond M.: Amer. Jour. Physiol., **144:** 284, 1945. (Courtesy of *American Journal of Physiology.*)

l it is seen that the average rate of disappearance of the white blood cells from the peripheral blood under these conditions was 881 cells per cu. mm. per hour. Table 2 is also taken from previously reported (17) work dealing with the output of lymphocytes in the thoracic duct lymph. If one takes the figure for the output of lymphocytes in the thoracic duct lymph and compares it with the number of lymphocytes in the peripheral blood, t will be found that the output is sufficient to account for the replacement of the lymphocytes every ten to twelve hours. These results are in agreement with those reported by Drinker and Yoffey (18).

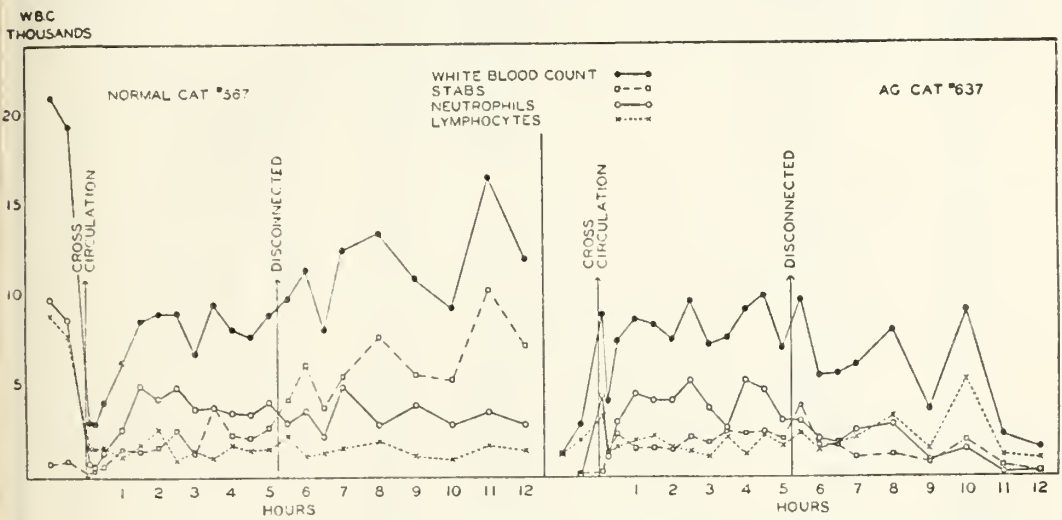


CHART 7. This chart shows the changes in the white blood cell picture of a leukopenic cat and a normal cat during and after cross circulation. The leukopenic cat had infectious feline agranulocytosis. Lawrence, John S., Ervin, Donald M. and Wetrich, Raymond M.: Amer. Jour. Physiol., **144:** 284, 1945. (Courtesy of *American Journal of Physiology.*)

If these observations can be carried to the human, and we think they may be, there is no need to postulate peripheral destruction since it will be only a few hours after the manufacture of the white blood cells has ceased before all of the cells have disappeared from the peripheral blood. However, the results do not exclude the possibility of peripheral destruction. In some instances, we feel that this mechanism does exist.

I should like to devote the remainder of the time at my disposal to a consideration of the treatment of leukopenia. It can readily be seen from the foregoing that the treatment depends primarily upon the type involved.

The most important single therapeutic procedure is to remove the cause whenever this is possible. In most instances, this alone will result in cure. As stated previously this has been universally true in our clinic in sulfonamide agranulcocytosis. I believe little trouble will be caused by drugs producing agranulocytosis if patients getting these drugs are watched carefully and the drugs discontinued when leukopenia first develops.

Various forms of therapy have been advocated for the relief of leukopenia. They can be discussed best individually.

1. Pentnucleotide and related substances. These drugs have been used extensively since they were first advocated by Reznikoff (19) and Jackson (20). I have never been convinced of their efficacy. They were used by us in the period from 1930 to 1935, but have been used less and less since then. We do not use them now, and, as stated, our results have been better in recent years. The good results are probably due to the nature of recent agranulocytosis and its early detection.

2. Transfusions. I doubt if any appreciable benefit is obtained by this procedure. Certainly, it is futile to attempt to raise the level of the white blood cells in the peripheral blood in this way. Perhaps some aid in combatting infection may be provided.

3. Liver extract. Powers and Murphy (21)

TABLE 1*

*Synopsis of Important Data in Cross Circulation Experiments (Experimental Group)*

| Cat Number | Type of Animal | Time of X† | Independent Circulation | White Blood Cells per c.mm. | | | | | W.B.C. Lost per c.mm. per hour |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Prior to X | Start of X | End of X | First after X | End of Experiment | |
| | | *hours* | *hours* | | | | | | |
| 7 | Irradiated | 21 | 8 | 300 | 9,100 | 6,650 | 3,800 | 250 | 538 |
| 16 | Normal | 21 | 9 | 15,500 | 9,200 | 2,650 | 4,400 | 6,000 | |
| 1 | Irradiated | 2½ | 21 | 250 | 15,600 | 15,300 | 11,800 | 100 | 618 |
| 18 | Normal | 2½ | 21 | 24,000 | 3,200 | 12,300 | 21,400 | 47,300 | |
| 19 | Irradiated | 3 | 7½ | 350 | 2,400 | 4,700 | 5,800 | 50 | 973 |
| 20 | Normal | 3 | 7½ | 13,000 | 550 | 3,950 | 9,300 | 23,500 | |
| 23 | Irradiated | 4 | 6 | 600 | 3,700 | 6,300 | 4,050 | 800 | 591 |
| 24 | Normal | 4 | 6 | 14,000 | 900 | 5,500 | 7,500 | 14,100 | |
| 25 | Irradiated | 2 | 9 | 250 | 8,500 | 9,400 | 10,000 | 100 | 1,213 |
| 26 | Normal | 2 | 9 | 19,500 | 1,200 | 9,500 | 14,400 | 19,800 | |
| 28 | Irradiated | 6 | 8 | 50 | 6,800 | 7,800 | 6,400 | 550 | 780 |
| 27 | Normal | 6 | 8 | 29,700 | 2,300 | 7,800 | 18,700 | 11,100 | |
| 29 | Irradiated | 16 | 2½ | 350 | 4,700 | 2,400 | 1,100 | 250 | 378 |
| 30 | Normal | 16 | 9½ | 13,800 | 2,100 | 1,400 | 2,800 | 20,800 | |
| 17 | Ag.‡ | 5 | 7 | 2,900 | 9,000 | 7,100 | 9,800 | 1,600 | 1,364 |
| 8 | Normal | 5 | 7 | 19,500 | 3,100 | 9,000 | 9,900 | 12,100 | |
| Total | | | | 154,050 | 82,350 | 111,750 | 141,150 | 158,400 | |
| Av. per cat | | | | 9,628 | 5,147 | 6,984 | 8,821 | 9,900 | |
| Av. % of change | | | | | *−46.5* | *−27.5* | | | |
| Total of 8 normals | | | | 149,000 | | | 88,400 | 154,700 | |
| Av. per normal cat | | | | | | | 11,050 | 19,337 | |
| Av. % of change (normal cats) | | | | | | | | *+75* | |
| 31 | Irradiated | 22 | 9 | 1,600 | | | 12,800 | 1,000 | 1,475 |
| 21 | Normal | 4 | | 14,300 | | | | 15,300 | |
| 32 | Normal | 8 | | 15,600 | | | | 18,000 | |
| 22 | Normal | 10 | | 14,000 | | | | 23,800 | |
| Av. W.B.C. per c.mm. per hour | | | | | | | | | 881 |

* Lawrence, John S., Ervin, Donald M., and Wetrich, Raymond M.: Amer. Jour. Physiol., **144**: 284, 1945 (Courtesy of *American Journal of Physiology.*)

† Cross Circulation.

‡ This cat had infectious feline agranulocytosis.

advocated this form of therapy in 1933. I have never been convinced of its value. It is possible that the small amount of folic acid in the liver extract may have been of some value.

4. Yellow bone marrow extracts. Watkins and Giffin (22) in 1933 reported good results from the use of strained yellow bone marrow in the treatment of agranulocytosis. Marberg and Wiles (23 and 24) have confirmed their results. Recently Caldwell et al. (25) have reported stimulation of leukopoiesis in benzene poisoned rabbits by extracts of yellow bone marrow. I have had no experience with this form of therapy.

5. Splenectomy. In 1942 Wiseman and Doan (13) reported a condition which they designated as primary splenic neutropenia. Splenectomy in such cases was reported as curative by them. It had, of course, been known for a long while prior to this that leukopenia of chronic congestive splenomegaly was relieved as were the other abnormalities of the blood in this condition by splenectomy. We have found this to be true in five cases of chronic congestive splenomegaly in our clinic. I would like to emphasize the fact that splenectomy is *not* a cure-all for diseases of the blood. Its use should only be resorted to in well selected cases. In most patients with leukopenia, splenectomy only adds an unnecessary operation.

6. Pyridoxine. Vilter, Schiro and Spies (26) reported in 1940 an increase in the white blood cell count in pellagrins with primary anemia following treatment with pyridoxine. Cantor and Scott (27) have more recently, 1944, reported a marked increase in three cases of agranulocytosis following the use of pyridoxine. Fishberg and Vorzimer (28) have reported spectacular results with this drug in agranulocytosis due to thiouracil. I have had little personal experience with this drug. In one case of marked leukopenia asso-

TABLE 2*

*Results of Thoracic Duct Cannulation of Twenty-one Normal Cats*

| Experiment Number | Duration | Lymph Flow | Average Lymphocyte Count of Thoracic Duct Lymph per cu. mm. | Average White Blood Cell Counts per cu. mm. | Average Number of Lymphocytes in Blood per cu. mm. | Thoracic Duct Lymphocytes in Millions per Kilogram per Hour |
|---|---|---|---|---|---|---|
| | *hours* | *cc. per hour* | | | | |
| 1 | 3.0 | 1.80 | 24,625 | | | 24.5 |
| 2 | 4.0 | 7.12 | 9,471 | | | 35.6 |
| 3 | 2.5 | 2.84 | 15,842 | | | 31.4 |
| 4 | 2.0 | 5.75 | 7,219 | 22,650 | 2,491 | 29.8 |
| 5 | 7.0 | 3.14 | 15,933 | 15,480 | 1,548 | 33.6 |
| 6 | 6.0 | 3.02 | 4,288 | 23,223 | 3,065 | 9.6 |
| 7 | 8.0 | 6.05 | 28,779 | 22,182 | 2,285 | 92.6 |
| 8 | 6.0 | 4.90 | 11,690 | 26,584 | 2,525 | 27.9 |
| 9 | 6.0 | 3.72 | 11,748 | 45,207 | 2,622 | 29.6 |
| 10 | 6.5 | 4.08 | 12,321 | 18,635 | 3,727 | 24.2 |
| 11 | 6.0 | 6.23 | 14,850 | 16,592 | 1,377 | 40.3 |
| 12 | 7.0 | 6.77 | 29,587 | 39,893 | 4,787 | 86.5 |
| 13 | 6.0 | 5.22 | 21,800 | 31,960 | 2,205 | 44.4 |
| 14 | 6.0 | 2.83 | 12,655 | 42,880 | 4,803 | 19.0 |
| 15 | 6.0 | 6.44 | 11,183 | 19,775 | 1,700 | 37.6 |
| 16 | 6.0 | 4.16 | 20,602 | 17,350 | 3,643 | 50.3 |
| 17 | 6.0 | 6.88 | 7,900 | 28,166 | 2,253 | 19.2 |
| 18 | 6.0 | 4.94 | 7,805 | 38,066 | 2,474 | 21.7 |
| 19 | 6.0 | 6.93 | 5,208 | 42,500 | 2,762 | 13.6 |
| 20 | 6.0 | 7.28 | 7,600 | 37,916 | 3,526 | 35.3 |
| 21 | 6.0 | 5.36 | 16,166 | 17,833 | 1,908 | 39.1 |
| Average..... | | 5.02 | 14,156 | 26,160 | 2,761 | 35.5 |

* Adams, William S., Saunders, Richard H., and Lawrence, John S.: Amer. Journ. Physiol., **144**: 297, 1945. (Courtesy of *American Journal of Physiology.*)

ciated with splenomegaly and in another patient with irradiation leukopenia, the drug produced no change in the white blood cell picture.

7. Sulfonamides. The use of these substances for combatting infections amenable to them in leukopenia was advocated by Dameshek and Wolfson in 1942 (29). We have treated three patients with agranulocytosis not due to sulfonamides with sulfadiazine. Two of these patients died and one recovered. The use of these drugs is logical and would, no doubt, be increased were it not for penicillin.

8. Penicillin. This anti-biotic has none of the dangers of the sulfonamide drugs as regards the effect on the blood picture. This substance was advocated for use in agranulocytosis by Dameshek in 1944 (30). Others have advocated its use since then (31, 32 and 33). There seems to me no logical reason for withholding this anti-biotic in patients with acute agranulocytosis. Certainly it offers much better protection than the individual would have otherwise.

9. Folic acid. That anemia could result from deficiency of factors of the vitamin B complex has been known for a long while. Smith, Reiser and Harrell (34) gave a good review of this subject in 1941. Day, Langston and Shukers (35) described anemia and leukopenia in the monkey given a diet deficient in the vitamin B complex. Day et al. (36) designated the deficient substance as vitamin M. Spicer and associates (37) reported the prevention and treatment of leukopenia produced in rats by a purified diet associated with injection of sulfonamides. Others (38 and 39) have reported similar results. Mallory et al. (40) have presented evidence showing that vitamin M and folic acid are the same or are closely related substances. Watson and his associates (41) have reported a favorable effect of folic acid on irradiation leukopenia in the human. The successful synthesis of folic acid has been reported recently (14). Following this, there has, for the first time, been sufficient amounts of the material for clinical trial. A series of clinical reports (42, 43, 44, 45, 46, and 47) has been made since then showing that primary anemia, tropical and non-tropical sprue and pernicious anemia of pregnancy respond readily to treatment with folic acid. The leukopenia as well as the anemia in sprue and primary anemia is corrected by this drug. We have obtained in our clinic spectacular results in patients with primary anemia treated with this substance. In these patients the white blood cell count promptly changes from a leukopenic level to a normal or elevated level following treatment with folic acid. We have not been able to confirm the work of Watson and his associates (41) in irradiation leukopenia in five patients. Fifteen milligrams of folic acid by mouth were given to these patients daily over a period of ten days. We have had no experience with the use of this drug in agranulocytosis due to drugs as we have had none of these patients since the vitamin was available. It is hoped, of course, that it will prevent agranulocytosis in thiouracil treated patients and that it will alleviate agranulocytosis when it develops as a result of other drugs or agents. Prolonged clinical trial will be required to settle this problem.

## Summary

1. A clinical classification of leukopenia has been given.

2. Clinical illustrations of some of the different types of leukopenia have been shown.

3. The importance of white blood cells in combatting infection has been stressed.

4. It has been pointed out that agranulocytosis due to drugs varies as regards sensitivity depending upon the particular drug responsible for it.

5. The rate of disappearance of the white blood cells from the peripheral blood has been shown to be very rapid.

6. The most important therapeutic procedures in leukopenia have been shown to be removal of and the early recognition of its cause.

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## Résumé

1. Une classification clinique des leucopénies fut démontrée.

2. Quelques variétés cliniques de leucopénie ont été exposées.

3. On a fait mention spéciale de l'importance des leucocytes pour combattre les infections.

4. Il fut démontré que l'agranulocytose secondaire à l'absorption de certaines médications varie selon la sensibilité de l'individu et que cette sensibilité dépend de la médication administrée.

5. On a démontré que la rapidité avec laquelle les leucocytes disparaissent de la circulation périphérique est très rapide.

6. Il fut également démontré que la meilleure thérapeutique contre la leucopénie se trouve dans un diagnostique précoce et dans l'arrêt immédiat de la médication.

R. Brault, M.D.

## Resumen

1. Se presenta en el artículo una clasificación clínica de las leucopenias.

2. Se dan ilustraciones clínicas de algunos de los principales tipos de leucopenia.

3. Se hace hincapié en la importancia de los leucocitos en el combate contra la infección.

4. Se ha señalado que la agranulocitosis debida a drogas varía con la sensibilidad individual dependiendo de la droga responsable.

5. La velocidad de desaparición de los leucocitos de la sangre periférica se ha mostrado ser muy rápida.

6. Los factores más importantes en la terapéutica de las leucopenias son reconocer temprano y eliminar la causa responsable.

J. M. Taveras M.D.

# Humoral Factors in Experimental Carcinogenesis*

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EXPERIMENTAL animals subjected to prolonged treatment with estrogenic hormones give rise, in several organs or tissues, to tumors that would not otherwise appear or that would appear at lower incidences. For example, mice subjected to estrogen for prolonged periods acquire mammary, lymphoid, testicular interstitial cell, pituitary or uterine cervical tumors under certain circumstances (1). Fibromatous tumors of the uterus and peritoneum appear in estrogen-treated guinea pigs (2). Estrogen-treated rats acquire mammary tumors and pituitary adenomas (3, 4). Mammary and uterine tumors appear among rabbits exposed to high levels of estrogens (5) or among rabbits of some stocks exhibiting a syndrome indicating a high level of production of intrinsic estrogenic hormone (6, 7). On the other hand it has been impossible to induce mammary or uterine cancer in monkeys by prolonged treatment with estrogens (8).

The above statements have, for the greater part, been adequately confirmed but they do not tell a complete story. Can it be said that, because of the above facts, estrogens are of etiological significance in carcinogenesis in man and furthermore if they are so related what can be done about it?

The negative experiments are of significance and interest. Monkeys treated with estrogens do not acquire mammary or uterine cancer even when the treatment is continued for 6 years or more (8). But mammary cancer has never been observed, to the writer's knowledge in monkeys of the species studied most extensively (Macacus rhesus); monkeys have no innate tendency to acquire such neoplasia, as far as can be judged from the available records. Under such conditions the estrogens have not been carcinogenic.

*Summary of a lecture presented on October 22, 1945 before the Section on General Medicine of the College of Physicians of Philadelphia and the Endocrine Society of Philadelphia.

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The studies leading to the discovery of carcinogenic hydrocarbons were instituted because it was assumed that some constituents of soot, tar or oils were responsible for the occupational cancers of the scrotum of chimney sweeps and mule spinners. The carcinogenic hydrocarbons derived from tars or prepared synthetically induce cancer in mice and rats at the sites of application (also at other sites in mice of some strains); animals of some strains are more susceptible than others, however. The hydrocarbons have not induced cancer in monkeys although some were treated for periods of many years (8). We can therefore say that the carcinogenic hydrocarbons and estrogens have not been shown active in experimental carcinogenesis in monkeys.

Mice of all inbred strains do not respond in the same manner to the carcinogenic action of estrogens or, for that matter, are not all equally susceptible to carcinogenic hydrocarbons. Estrogen-treated male mice or virgin female mice of some inbred strains acquire mammary cancer when estrogens are injected in appropriate amounts, but untreated breeding females of these strains also acquire mammary adenocarcinomas (1, 9, 10, 11). In other words the tendency for cancer is present in mice of these strains but is manifest only when the humoral environment is adequate—either by intrinsic production of hormones or by the injection of extrinsic hormones. It is now known that a proper genetic background, and the mammary tumor inciter or virus transmitted through the milk (12), must be present as well as hormones for at least one type of mammary carcinogenesis in mice.

Even when all of the above three factors are present the incidence of mammary cancer can be kept very low by the injection of the androgenic hormone, testosterone propionate, a point of considerable interest but of questionable practical value because of the large size of the doses and prolonged periods of treatment required (13, 14).

Lymphoid tumors probably appear in mice of all strains but in most of them the incidence is low, approximately one per cent. Among seven strains

of mice estrogen-treatment increased the incidence approximately fifteen times in 3; it had less effect in 2; and no effect in 2 (15). The differences cannot be accounted for at this time except on the basis of different genetic susceptibilities to estrogen-induced lymphomatosis. The mice of the strains susceptible to estrogen-induced lymphomatosis under the conditions of the experiment transmitted the tendency for lymphoid tumors to their hybrid young when they were crossed with non-susceptible strains (16). Androgens inhibit the lymphomagenic action of estrogens (15).

Tumors of the interstitial cells of the testes that metastasize to lumbar and renal lymph nodes, develop in mice of a few strains when estrogens are given for extended periods although such tumors appear with extreme rarity in untreated mice (17–20). Some of the progressive series of morphological changes occur in the testes of mice from the resistant as well as the susceptible strains but tumors do not appear in the former (19). The tendency for mice to acquire testicular tumors subsequent to estrogen treatment is transmitted by both males and females to their hybrid young.

Chromophobe adenomas of the pituitary occur in estrogen-treated mice from one of the 9 strains studied in this laboratory although spontaneous hypophyseal tumors have never been observed in these strains (21). Some of these tumors are very large and grow subsequent to transplantation but only in estrogen-treated hosts.

Carcinomas of the uterine cervix or upper vagina have been observed among estrogen-treated mice of several inbred strains although such tumors have never been detected in untreated mice of these strains (22, 23). Uterine cervical or upper vaginal carcinomas have appeared among mice of one strain that exhibits a high incidence of a genital anomaly (imperforate vagina); an anomaly that indicates hormonal imbalance (24). In this strain there may be a genetic tendency for a hormonal imbalance that favors the development of cervical tumors or, possibly, for the development of such tumors independently of the humoral environment.

Even in mice one cannot expect animals that are genetically unrelated to respond in the same manner to the tumorigenic action of estrogenic hormones as indicated above. It is not too unreasonable to assume that among the heterogeneous human population there are some individuals in whom tumors might be induced by application of estrogen and others in whom such would not be the case. The levels of intrinsic hormones may be adequate in some to bring out latent tumorous tendencies in some persons but not in others. At least it is known that man does acquire tumors of these types, especially those of the female genital tract.

The mammary, lymphoid and uterine cervical cancer grow in other mice of the same strain subsequent to transplantation and independently of the humoral environment in the host. Hormonal therapeutic measures have been of no avail after the tumors appear although, as stated above, testosterone generally inhibits or delays the assumption of the malignant process originally. Among experimental animals, with a few exceptions (mammary tumors in rats (25) and fibromatous tumors in guinea pigs) it has not been noted, as yet, that hormones can be used as chemotherapeutic or palliative agents as in some cases of mammary cancer in old women (26) and in some patients with prostatic carcinoma (27). It is of interest and significance that hormones which provide an environment favorable for the development of specific tumors in some species create an environment unfavorable for the progressive growth of tumors in other conditions, at least in some individuals. Until more information is made available both from the experimental laboratory and clinic, the carcinogenic or therapeutic action of estrogens in animals of each species or strain, and in each patient must be considered as unknown until tested and considered in relation to other predisposing etiological influences. At the present time it seems probable that in man only cancer of the uterine fundus and uterine fibroids are associated with evidence of *unusual* hormone production (28, 29).

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COLLEGE OF PHYSICIANS
OF PHILADELPHIA

# The Combined Injection of Vitamins and Vaccines, with a Note on Typhoid Agglutination Titres*

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THIS report presents evidence that the effect of vaccine is altered by vitamins added to the vaccine injected intradermally.

Group I. When typhoid, paratyphoid A and paratyphoid B vaccines[1] have been separately injected each in combination with a different vitamin, and frequent agglutination titres have been read, in some patients the titre rose more rapidly with the vaccine that, for example, had been combined with riboflavin; in others the most rapid rise occurred with the vaccine that had been injected with sodium ascorbate; in others again, with niacinamide. This suggests that individuals differ in this one phase of immunological response, agglutination, with different vitamins; that is, vitamins modify agglutination titres. The effective vitamin varies with different persons.

Individuals differ likewise in the amount of vitamin that combined with the vaccine causes a rise in titre.[2] Furthermore, in most patients vary-

TABLE 1

| | A | B | C |
|---|---|---|---|
| | Abrupt or sharp steady improvement | Slower but decided improvement | Not improved |
| 1. Relapsing pneumonia | 6 | (P. 2) 9 | 2 |
| 2. Chronic bronchopneumonia; residual x-ray density | 21 | (P. 3) 6 | (P. 3) 4 |
| 3. Probable bronchopneumonia; grouped rales | 10 | | |
| 4. Recurrent bronchopneumonia (x-ray) with iritis | 2 | | |
| 5. Bronchitis, chronic, recurrent | 22 | 8 | (P. 1) 2 |
| 6. Bronchitis, single attack, but persistent | 6 | | |
| 7. Bronchitis with arthritis, sciatic, or sacro-iliac pain | 5 | | |
| 8. Broncho-pleural fistula: 6 years duration—healed | | 1 | |
| 9. Lung abscess & empyema (1) 9 mos. (2) 11 mos. | 1 | (P. 1) 1 | |
| 10. Empyema—2 years duration | 1 | | |
| 11. Lung abscess: sub-acute | 1 | | |
| 12. Sinusitis | | | 3 |
| 13. Bronchiectasis | | (P. 1) 6 | 2 |
| 14. Infectious asthma | 2 | 3 | (P. 2) 6 |
| | 77 | (P. 7) 34 | (P. 6) 19 |

*Note.* (P. 1) (P. 3) shows number receiving penicillin during febrile exacerbations. All were temporarily, none permanently improved.

* Delivered before the Section on General Medicine of the College of Physicians of Philadelphia, April 22, 1946.

Editorial and research assistance has been given by Eleanor S. Cooper, A.B.

[1] T. A. B. vaccines were used occasionally in respiratory but chiefly in tuberculous cases, partly as a guide to the amount of vitamins to be combined with tuberculin.

[2] Rarely, the titre rose higher with no vitamin in combination.

ng the proportion of vitamin and vaccine causes a drop in titre with doses continued at weekly intervals; and this occurs without causing febrile reactions. The amounts of vitamins, of, e.g., niacinamide, have varied between one micromilligram and 0.01 mg., less often up to 1 mg., and the amounts of the three separate vaccines, typhoid, paratyphoid A and paratyphoid B, injected intradermally (1) (2) at each observation, varied usually from 1 to 20 million organisms. Insofar as agglutination (3) (4) (5) constitutes an immune response, it is significant that at least three vitamins cause these changes in titre frequently observed within more than 2000 readings.

Group II. Respiratory vaccines were combined with vitamins to treat cases of disabling chronic bronchitis, relapsing pneumonia and bronchopneumonia, and bronchiectasis (table 1). The evidence of vaccine efficacy rests largely upon the relation of the length of illness before treatment to the length of treatment: Symptoms lasting for months or years may be checked in a few days; often within one day. The recovery may continue after several doses; in other cases, symptoms, though abated, recur some 6 days after treatment. In many cases with severe old lesions (usually in the cardiophrenic angle) re-infection recurs in this field of poor drainage (6).

Other arresting evidence: If vaccine is given in an amount that in itself does not cause symptoms, and if the larger amounts of vitamins are added, e.g., 1 mg. niacinamide per intradermal bleb, 1 mg. sodium ascorbate, 0.1 mg. riboflavin, in febrile patients with chronic infection, symptoms will usually increase within one day. Accordingly it appears that resistance is related to small amounts of vitamins, and pathogenicity to larger amounts when vitamins are injected intradermally, combined with heat killed suspensions of microorganisms.

Verification of these observations would amplify working hypotheses for study of resistance and of tumor metabolism.

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# Urinary Tract Pathology Engendered by Changes in the Generative System*

*By* J. MASON HUNDLEY, JR., M.D.

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AS CAN be readily understood the presentation of such a comprehensive topic requires the elimination of many of the self evident phases which are so well covered in the various gynecological textbooks.

With us female urology is a division of gynecology for by this union we feel the gynecologist is well fitted for the evaluation and treatment of urological problems in women. It is not uncommon for a patient with frequency and dysuria to have the bladder and trigone treated while the causative factor is a moderate sized myoma on the anterior uterine wall.

The subject will be discussed in relation to the three most important etiological factors. The first and probably the most important is the changes produced by pressure. Several years ago we published an article on the physiologic changes occurring in the urinary tract during pregnancy and as these changes are so frequent and typical a brief review of this work will be of value for lessons here learned also apply to other etiological factors which are of a pathologic nature. We carried out a urographic study of twenty-seven normal women throughout the succeeding months of gestation and the puerperium. In summary there was noted a dilatation of the pelvis and calices of one or both kidneys, a dilatation, tortuosity and kinking of one or both ureters and lateral displacement of these structures. In addition there was an apparent atony of the ureteral musculature. Every patient showed some deviation from the normal, the right kidney and ureter being more affected than the left. With the advance of pregnancy the dilatation of the upper tract gradually increased to the time of delivery and following this event there was a rather rapid regression to the normal state, taking place as a rule in twenty-eight days. The presence of infection greatly retards this process. In this study there was found a decrease of excretion time and an increasing atony of the ureter. We believe dilatation is due to two factors; first, changes in the ureter due to hormonal stimulation as shown by muscular hypertrophy, increased vascularity and loss of tone. This changed tube is then subjected to the pressure of the semicystic pregnant uterus. If the hormonal changes had not first intervened the semicystic uterus could not have affected the dense fibrous ureter.

Histologic changes are most striking in the ureter during pregnancy, mainly those of hypertrophy of the musculature, increased vascularity with dilatation and softening. The right ureter is most frequently involved due to its crossing the pelvic brim at nearly right angles thus making it vulnerable to the pressure of the dextrorotated uterus. The left ureter runs a straighter course and is cushioned by the overlying sigmoid.

Confirmatory evidence that pressure was one of the causative factors in ureteral dilatation was portrayed by the marked regression noted in the tract with the use of continuous drainage. These changes were brought about by using an indwelling catheter for period of forty-eight to seventy-two hours.

Is there sufficient proof that the urinary tract is subject to hormonal stimulation? We feel there is. The urinary tract and generative tract arise from the same anlage and we believe that both systems are affected by the same hormonal influences elaborated during gestation. Note the marked hypertrophic changes in the musculature loss of tone and marked atony. We observed these same changes in a man who had a teratoma of the testis with metastatic chorio-epithelioma. Several pregnancy tests were positive. The muscular hypertrophy in the juxta vesical region was even more marked than during pregnancy.

Another factor that supports these hormonal changes is the rapid regression of the dilatation with the delivery of the placenta, the main source of estrogenic and anterior pituitary-like substance. To determine the changes of ureteral activation during pregnancy we recorded graphs with Trattner's hydrophorograph and found with the advan-

* Read at the joint meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia, Jan. 9, 1946.

of pregnancy there was an increasing loss of tone and a gradual allaying of all muscular activity so that the tube was quite inert. However just before parturition there was a return of ureteral activity.

After carrying out this study of ureteral behavior during pregnancy we attempted to produce the same effects in the ureters of the non-pregnant woman by the administration of estrogenic substances and progestogenic substances. We know that estrogens cause muscular contractibility and progestogens allay this activity. By priming normal women with large and prolonged doses of these substances we hoped to simulate in a measure hormonal conditions that exist during pregnancy and possibly produce the same ureteral behavior that normally occurs during this period. A group of nonpregnant women were given large doses of Stilbestrol daily over a period of ten weeks, each receiving 280 mg. Weekly hydrophorographic tracings were made and there was noted a great increase in peristaltic activity.

In order to determine if allaying of ureteral activity and final atonia developed under the influence of progestogenic substances another group of normal nonpregnant women were selected for observation. These women received intensive courses of progestogenic therapy over a period of nine weeks each receiving a total of Proluton 72 mg. and Pranone 2.520 mg. In a short time there was noted marked diminution of ureteral peristalsis and eventually complete allaying of all activity thus simulating the same condition as occurs during the latter weeks of pregnancy.

What effect do ovarian and uterine tumors have upon the urinary systems? In a previous publication we have shown that dilatation effects due to pressure are of common occurrence as is to be expected, the denser the tumor and more it conforms in size to a pregnant uterus the more pressure effects will be noted.

Another cause of dilatation of the tract is due to bilateral carcinoma of the parametria arising from the cervix. Approximately 65% of the patients in our oncological clinic had parametrial involvement. With potential associated degenerative changes in the kidney a common symptom in this group is nausea and vomiting with increasing N.P.N. and eventually uraemia and even anuria. The dilatations of the tract are often bilateral and begin at the bladder.

The second most important factor is the pathology of the urinary tract as a result of parturition. These lesions are produced by difficult and multiple pregnancies with resulting relaxations, malpositions of the pelvic organs and occasionally fistuli due to pressure necrosis. In this group cystoceles and uterine prolapsus produce the important changes in the urinary tract. As is so well known a sacculated bladder frequently is associated with cystitis and with procidentia hydroureter and hydronephrosis are not uncommon.

Stress incontinence which is characterized by involuntary spurting of urine on stress or strain, even laughing or coughing may produce this condition. This type of incontinence is of frequent occurrence and is seen in postmenopausal women with a normal appearing urethra but with an associated trigonitis and regressive changes due to hypoestrinsim. Topical application of silver nitrate solution, 2–3% through the Kelly cystoscope is of great value. As many of the patients are highly neurotic mild sedation is necessary.

Stress incontinence is also seen as a result of obstetrical trauma with associated relaxations and loss of sphincter tone. Dr. Howard Kelly in 1911 stated that the key to successful treatment of this condition lies at the internal orifice of the urethra and in the sphincter muscle which controls the canal at this point. The main steps in the operation which he described consists of a high advancement of the bladder well up on the cervix with suturing of the torn or relaxed tissues at the neck of the bladder so as to buttress the vesical neck.

Another important factor to be considered is the role of adnexal and cervical infections as they pertain to the urinary system. Adnexal disease of the chronic type with masses causes compression effects upon the ureter and according to the study of Everett and Sturgis are of frequent occurrence. The work of Martin Schreiber upon the subject of ureteral stricture, based on the findings in one hundred consecutive autopsies, is of particular interest. A partial summary of his conclusions are as follows:

1. Stricture of the ureter does exist as a definite pathological entity.

2. A 12% postmortem incidence of stricture or stenosis corroborates the great number of such lesions found clinically.

3. Latent hydronephrosis due to obstruction are relatively frequent as evidenced by autopsy showing an incidence of 10%.

4. Ureteral stricture as a localized intrinsic

inflammatory process in the ureteral wall due to focal infection is rare.

5. Etiological factors. Extension of inflammatory process from adnexal disease.

6. Advanced chronic cystitis; narrowing of congenitally constricted site.

The incidence of stricture varies greatly with personal interpretation. Some rely on the "hang" produced with the wax bulb others on the finding of dilatations as shown by the urogram. As a rule we rely greatly on the X-ray findings. However we all know that patients are frequently relieved of their symptoms following dilatation of the ureter even when the urograms showed no abnormality.

Knowing that a considerable difference of opinion exists as to the relationship of endocervicitis to trigonitis and cystitis we cystoscoped a group of 50 women who had varying degrees of cervicitis. In order to designate the extent of the lesion they were classified from 1 plus to 4 plus accordingly there were found 13 patients with 1 plus lesions, 19 patients with 2 plus lesions, 13 patients with 3 plus lesions and 5 patients with a 4 plus lesion.

In this group of 50 women the bladder symptoms complained of were as follows: Nocturia 10 times, dysuria 10 times and in 32 patients there were no urinary complaints.

A summary of the cystoscopic findings are as follows: Bladder mucosa normal in 47 patients. Ureteral orifices normal in 45 patients. Trigone normal in 34 patients. Slight degrees of injection were found in 13 and in only 3 was there a definite trigonitis. Bladder cultures were taken in all but 4 patients and 48% of these were found positive. The usual nonpathogenic organisms which inhabit the vestibule and vulva were found. We feel that these organisms enter the bladder through the short patulous urethra or are introduced with even the most careful catheterization. This finding of 48% positive cultures of the bladder corresponds closely to the findings observed in a previously published bacteriological study of the bladder and kidney urines of the normal pregnant and nonpregnant woman.

From this study we feel that we can draw the following conclusions:

Endocervicitis plays no role as a causative factor in the production of cystitis. It would seem the same holds true for trigonitis for here the trigone was quite normal in 34 patients and there were found slight degrees of injection in 13. As is well known the evaluation of the trigone as to the degree of hyperemia and whether the mild changes are normal is very difficult. From this study we feel there is no significant relationship between pathology of the cervix and bladder.

If there is a lymphatic pathway as some claim why does not cervical carcinoma invade the bladder more frequently. We cystoscoped 413 patients with such malignancy and found bladder involvement in only 13.1%.

We have here attempted to present the more interesting and debatable features of this large subject but have been forced by lack of time to leave out consideration of various subjects such as involvement of the bladder by ectopic endometrial tissue which may occasion monthly haematuria

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## Résumé

La discussion du sujet se porte sur les trois plus importants facteurs étiologiques:

Le premier et probablement le plus importa de ces facteurs se rapporte aux changements qu produit la pression. L'auteur fait mention de s publication précédente dans laquelle il faisa remarquer que durant la grossesse, il apparait un dilatation du bassinet et des calices d'un seul c des deux reins; une dilatation, une tortuosité une coudure d'un seul ou des deux uretères; ain qu'une déviation latérale de ces organes et un atonie apparente des uretères. On semble a tribuer cette dilatation à certaines modificatio urétérales secondaires à une stimulation hormona Ce conduit urinaire est alors assujetti à la pressi exercée par l'utérus gravide qui a alors une co sistance semi-cystique. Les tumeurs utérines ovariennes ainsi que l'épithelioma du col utéi avec extension bi-latérale aux ligaments larg

sont aussi des causes de dilatation des voies urinaires.

Le deuxième facteur consiste en des lésions traumatiques provoquées par les grossesses répétées et laborieuses. Il s'agit de relachement et de déviations des organes pelviens, ainsi que de fistules secondaires à la nécrose des tissus par pression prolongée. Le cystocèle et le prolapsus utérin sont considérés dans ce groupe comme les maladies qui donnent les modifications les plus importantes des voies urinaires. L'application locale de nitrate d'argent à 2 ou 3 pour cent dans la vessie avec le cystoscope Kelly et l'usage de sédatifs doux donnent de bons résultats dans le traitement de l'incontinence d'urine qui survient au moment des efforts, du rire ou de la toux. L'opération suivant la méthode de Kelly pour effectuer la cure chirurgicale de l'émission involontaire d'urine au moment des efforts est brièvement décrite.

Le troisième facteur qui fut considéré est le rôle que jouent les infections cervicales et annexielles. On a aussi démontré la part que jouent les annexites chroniques avec masses pelviennes dans le compression des uretères. Un résumé des conclusions de Schreiber fut également décrit. Hundley vint à la conclusion que, d'après ses études cystoscopiques récentes, il n'existe pas de rapport important entre les conditions pathologiques du col uterin et celles de la vessie.

R. Brault, M.D.


## Resumen

Se discute el asunto en relación con los tres factores etiológicos de más importancia.

El primero y probablemente el más importante es los cambios producidos por compresión. El autor se refiere a su observación previamente publicada de que en el embarazo hay una dilatación de la pelvis y cálices de uno o ambos riñones, una dilatación y retorcimiento de uno o ambos ureteres, y desplazamiento lateral de estos junto con atonía de la pared ureteral. La dilatación se cree debida a cambios en el ureter causados por estímulo hormonal, asociados con la compresión causada por el útero grávido. Otras causas de dilatación son los tumores del ovario y del utero y el cáncer bilateral de los parametrios debido a carcinoma primario del cuello uterino.

El segundo factor de importancia se encuentra en las lesiones causadas por el parto. Estas lesiones son producidas por embarazos repetidos y difíciles resultando en la relajación y posición viciosa de los órganos pélvicos y a veces en la formatión de fístulas debidas a necrosis producidas por compresión. En este grupo, los cistoceles y el prolapso uterino producen los cambios más importantes en el sistema urinario. Aplicaciones locales de nitrato de plata al 2 ó 3 por ciento por medio del cistoscopio de Kelly, accompañadas de sedantes suaves, es de gran ayuda en el tratamiento de las incontinencias de orina causadas por esfuerzo. La operacion de Kelly para la incontinencia de esfuerzo causada por traumatismos obstétricos se describe brevemente en el texto.

El tercer factor de importancia es el papel de las infecciones anexiales y cervicales. La frecuencia de los efectos de compresión sobre el ureter causadas por enfermedad cronica de los anexos con formación de masas, está demostrada. Un resumen parcial de las conclusiones de Schreiber sobre las estrecheces ureterales se presenta en el texto. Hundley concluye, en su reciente estudio cistoscópico, que no hay una relacion significativa entre la patología del cuello uterino y la de la vejiga.

J. M. Taveras, M.D.

# The History and Growth of the Mütter Museum

*By* ELLA N. WADE

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THE Museum of the College of Physicians of Philadelphia was first known as "The Museum of Pathological Anatomy," and, like the College, had no real home until it moved into the building at 13th and Locust Streets which was completed in 1863. At that time the museum of Dr. Thomas Dent Mütter was added to it and it became the "Mütter Museum."

Dr. Isaac Parrish seems to have been the moving spirit in the founding of the Museum, and responsible for its initial growth, for donations were more numerous from the time of its inception until his death in 1852 than they were in the ten years following. At the end of those first three years the case contained sixty-seven pathological specimens.

It is recorded in the minutes of the stated meeting of the College of June 5, 1849, that Dr. Isaac Parrish presented a preamble and resolution proposing the institution of a Pathological Cabinet under the control of the College, "to facilitate the promotion of science, and secure to the profession a valuable amount of material of this kind which would otherwise be lost." Drs. Isaac Parrish, John Neill, John Bell, Henry H. Smith and Edward Hallowell were appointed a committee of five to consider the proposal. On June 9, 1849 they submitted a report in which they agreed that immediate steps should be taken to establish this new addition to the College in the interest of science.

The Museum of Pathological Anatomy was to be under the direction and control of the College through an appointed committee, and a gentleman qualified for the duties, who would be willing to fill the position gratuitously, was to be appointed to act as curator.

At the same time it was proposed that a sum not exceeding fifty dollars be appropriated for the necessary cases to house the exhibits.

A Pathological Cabinet was erected at a cost of twenty-five dollars, and on October 2, 1849, Dr. John Neill was elected curator, and Drs. Moreton Stillé, Edward Hallowell and Isaac Parrish were elected members of the Museum Committee.

Dr. Joseph Parrish, father of Dr. Isaac Parrish, had accumulated a large number of pathological specimens, which he had used in illustrating his lectures, and many of these were presented to the Museum by his son, forming the nucleus for the collection which increased rapidly by additions from other sources. Drs. H. B. Coates, John Neill, Henry H. Smith and George W. Norris were among these early contributors.

We regret to state that of the first twenty-four specimens presented to the Cabinet, we have record of but four still remaining in the Museum. Several, however, answer the description of these donations although they bear no donors' names, so it is reasonable to suppose that they are the original specimens from which labels were lost when moving from one building to another.

The College was particularly active in matters of scientific interest in 1849, and one subject that engaged its attention was epidemic cholera. The members desired to obtain accurate information on the condition of the mucous membrane of the intestinal canal in persons dying of this disease. A committee consisting of Drs. Samuel Jackson, John Neill, Henry H. Smith and William Pepper was appointed to undertake this investigation.

Since it was apparent from previous experience that ordinary examinations had failed to give adequate and useful information, the committee felt that specimens should be injected and inspected with the microscope. Twenty-five specimens of intestines were prepared in this manner for microscopic examination by Dr. John Neill, who at that time was demonstrator of Anatomy at the University of Pennsylvania and also physician to the Southeast Cholera Hospital. Twenty-one of these specimens subsequently became a part of the Museum collection where they are still on display.

The gentlemen, after their examination and report, still were not entirely convinced that the changes they found in the mucous membrane of the intestines were characteristic of cholera, so the committee was continued to make further comparative examinations, the results of which never seem to have been recorded.

After the death of Dr. Isaac Parrish in 1852, the Museum appears to have undergone a period of inactivity. Abundant clinical cases were illustrated

at the College meetings, but few of the specimens found their way into the Museum until 1863 when the entire Pathological Museum of Prof. Thomas Dent Mütter was annexed to it.

Doctor Mütter died in 1859 at the age of forty-eight, but in that short space of time he bequeathed a museum, founded a lectureship, and became known for his skill in plastic surgery.

He was graduated from the University of Pennsylvania in 1831 and studied for one year in Europe. Upon his return in 1832 he devoted himself to surgery, instituted plastic treatment for disfigurations arising from burns, and operated successfully to minimize congenital deformities. He was made Professor of Surgery of the Jefferson Medical College in 1841, but in 1856, because of ill health, was forced to resign. It was at this time that he made known to Dr. S. Weir Mitchell his desire to give the collection, which he had accumulated over a period of twenty-four years, and which he valued at over $20,000 to the College of Physicians, on condition that a suitable fireproof building would be provided for it, agreeing to keep the Museum in order at his own expense during his lifetime.

At his death a bequest of $30,000 was to go to the College also, to increase and maintain the Museum, and to pay the salaries of a curator and lecturer.

In 1856 the proposition was favorably considered by a committee, but because of the serious responsibilities placed on the College, a further conference with Doctor Mütter was necessary. Much to his disappointment, however, no conclusion was reached, due in part to the fact that although a building fund had been started in 1849, there were not sufficient funds available for the erection of a "suitable fireproof building," and as he expressed himself "too ill and too busy" to give further attention to the matter, the committee was disbanded until 1858. Then Doctor Mütter informed Dr. George B. Wood that he was ready to go through with the original plan, and the agreement was signed by the College and himself, and the erection of the new building at 13th and Locust Streets was begun.

Doctor Mütter did not live to see it completed, but his wishes were carried out and on January 6, 1864, his collection consisting of 1139 specimens, 200 casts, 48 oil paintings and 364 water color drawings, was removed from the Jefferson Medical College, united with the one hundred pathological and anatomical specimens of the College, and Dr. Thomas G. Morton became the first paid curator of the Mütter Museum, and Drs. John R. Paul, William Hunt and S. Weir Mitchell became the first committee to serve under the new order.

The years following, especially the period from 1872 to 1885, were years of prosperity and growth for the Museum. Individual specimens and entire personal collections were donated, and thousands of dollars of the income from the Mütter legacy were spent for valuable specimens. Dr. Thomas Hewson Bache, who served as curator from 1865 to 1884, personally scoured the European markets for the best museum material available, and also purchased rare specimens brought to the attention of the committee by Fellows of the College who were keenly interested in the growing institution.

It was in 1874 that we acquired the famous Hyrtl collection of skulls of all races, the corrosional preparations and the labyrinths and ossicles of the ear of man and all mammalian families.[1]

In 1875, Dr. Joseph Leidy procured the body of the "Petrified Lady"[2] for the Museum, and the following year, while in London, took the responsibility of purchasing for it a male and female gorilla skull, both of which exhibit evidence of caries.

In the same year, also, Professor Adam Politzer's series of tympanic membranes were purchased, or rather we should say the Museum purchased the material incidental to mounting and exhibiting them. They were prepared by Professor Politzer himself, and sent to the Centennial Exhibition of 1876. He was attacked later for selling specimens obtained from his patients at the Old People's Home, and a caricature of him as a Jew peddler hawking baskets of human specimens, was published. He wrote to the College of Physicians asking them to certify that he had refused to *sell* the specimens which he had *given* to the Museum, but had let us pay $800 for their mounting and display. This the College obligingly did.

The imposing skeleton of the Mütter American Giant[3] was purchased for the Museum in 1877.

[1] *Cf.* Wade, E. N. Letters from Prof. Hyrtl found in a Mütter Museum scrapbook, *Trans. & Stud. Coll. Phys. Phila.*, 4th ser., **12**: 115–118, 1944–45.

[2] *Cf.* McFarland, Joseph. Rummaging in the museum. II. The petrified lady, *Trans. & Stud. Coll. Phys. Phila.*, 4th ser., **10**: 138–143, 1942–43.

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This was also obtained through the interest of Dr. Joseph Leidy who was informed by Professor A. E. Foote, a physician who renounced medicine to conduct a profitable business in Philadelphia selling minerals and rare books, that "the body of a giant was offered for sale provided no questions were asked which might lead to its identification." The arrangements were made and Doctor Foote received $50.00 and we received the giant.

In 1882, six adult skeletons, ten fetal skeletons and a fetal skeleton exhibiting anencephalia and spina bifida were purchased from J. V. Rohon, who was able to obtain material easily since he had free access to the Pathological Institute in Vienna.

The names, age, type of employment and, in most cases, the result of dissection accompanied these six adult skeletons, making them as intriguing as the figurative ones of Aunt Emma or Uncle Henry that are harbored in many a family closet. When I look at the perfect little skeleton of Rosa Heikl, aged twenty-four, of Bohemian descent, who was employed in the manufacture of artificial flowers, I am apt to disregard it as an anatomical specimen and picture a pretty girl in the bright dress of the Bohemian, working deftly and swiftly among her gay artificial blossoms, and, seeing one of the male skeletons, I am likely to ponder upon the misfortunes of the living Franz Reichberger, a forty-seven year old laborer, who probably was frequently absent from his daily toil because of ill health, for we read that he suffered from tuberculous ulcers and catarrhal phthisis of the colon and suppurative peritonitis.

Unhappy and miserable indeed must have been the lot of many of the individuals whose skeletons or portion of skeletons rest in our Museum cases, for so cruelly deformed are many of the thoraces, that it seems incredible that the internal organs, cramped and compressed as they must have been, were able to function normally enough to allow the person to reach maturity.

Six adult skeletons were also donated to the Museum by Professor George McClellan, a famous Philadelphia anatomist and Fellow of the College, who was, perhaps, interested in its growth because he served on its committee for six years.

Among the thirty-six complete skeletons in the collection is an interesting and unusual one presented by the Philadelphia Obstetrical Society about 1879. It is the skeleton of a rachitic dwarf, holding the skull of the fetus that had been removed from her by Cesarean section. This skeleton shows an unusual deformity of the pelvis. Also, the sacrum, instead of being curved, is straight, and goes directly backward, so that in front view it seems to be entirely absent.[4]

In 1882 the committee on the Museum purchased from Tramond of Paris, five cases containing wax models of maladies of the eye. These are excellent models and always attract the attention of visitors, especially students of the Pennsylvania State College of Optometry, who very often borrow the Museum's very rickety step-ladder in order to see those in the uppermost cases.

Primitive trephining is illustrated by the nineteen facsimiles of the Muñiz Collection of Peruvian skulls[5] purchased at this time. They were brought together by Señor Manuel Antonia Muñiz, M.D. Surgeon-General of the Peruvian Army, and exhibited at the World's Congress of Anthropology held in connection with the Columbian Exposition at Chicago. They represent three types of operations. The third operation, which appears to have been performed by scraping with stone to remove the outer table and diploë, seems a slight improvement over the first and second types, where deep incisions were made in the cranium by bits of stone and rectangular and elliptical buttons removed. Surprisingly enough, five of the skulls show evidences of the subjects surviving what must have been operations far more painful than the aches for the curing of which the operations were performed. A headache might be preferable.

It is rather difficult for a curator and committee in these lean years, when, because of a substantial shrinkage of the Mütter income, the spending of a few dollars for such small items as a Museum jar or a new lock for one of the cases, must be carefully considered, to picture the activities of a curator and committee during a prosperous era. Then their concern was with the selection of suitable material, and not with the ability to pay for it. The purchase, however, of fine museum specimens at a time when they were available, and when the finances of the Museum could well afford them, has contributed in making it the fine pathological and historical museum that it is today, so while we regret that the present officers must sometimes seem penurious, we do not begrudge the curators

[4] *Cf.* Walsh, J. F. The skeleton of a rachitic woman, and the skull of the fetus that had been removed from her by cesarean section, *Am. J. Obstetrics*, **12**: 766-770, 1879.

[5] *Cf.* McGee, W. J. Primitive trephining, illustrated by the Muñiz Peruvian Collection, *Bull. Johns Hopkins Hosp.*, **5**: 1–3. 1894.

nd committees of by-gone days the pleasure they ıust have experienced in the delightful task of reely and advantageously spending someone else's ıoney.

Many of the wet preparations in the Museum re from the original Mütter collection, but about n equal number came from other sources. They onsist of an embryological group showing the arious stages in the development of the embryo; a ollection of fetuses showing anencephalia, spina ifida, gastroschisis and hydrocephalus; a comaratively small number of anatomical specimens, ut a great number illustrating morbid anatomy, bout three hundred of which are different types f tumors. Some of these growths are enormous, nd I believe that surgeons sometimes after operatng for an especially large tumor, jokingly remarked hat they had removed Mrs. Jones from the tumor, ather than the tumor from Mrs. Jones. Probably Mrs. Jones failed to see any humor in it.

It is interesting to note the growth of the Muum in the different types of containers used when reserving a specimen, each type representing a ifferent period. The oldest type seems to be the ottle with an ordinary cork. Later the cork was eplaced by a glass stopper. These were hard to emove and often an attempt to do so resulted in reaking the jar or the stopper. Then came the ide-mouthed jar with the zinc or soft lead top ver which parchment was stretched and cemented. his was a very satisfactory way of making an ir-tight seal, for few jars closed in this manner how any evaporation over a period of seventy ears or more. Many of the jars in the Museum re the kind having a glass lid clamped to the jar ith a metal clamp, and made air-tight by a gasket r rubber very much like an ordinary fruit jar. hese are not entirely satisfactory for they freuently develop cracks around the neck for no pparent reason, not enough pressure may be pplied to the metal clamp to make a tight seal, nd the rubber softens and falls against the inside f the jar in a sticky mass which is difficult to emove. These gaskets are unobtainable as the ars are no longer made, and without them the jar s even less efficient.

The newer type of museum jar is square or ectangular and has a flat glass lid cemented to the op. In these, distortion of the specimen is elimnated and the lids may be made fairly tight if roper cement is used.

Formaldehyde has replaced alcohol as a preervative and the modern method produces attractive specimens in natural color. All of ours, being very old, are bleached and we have received no new material.

In the 1800's specimens were preserved whenever available, for there were few autopsies performed and material was hard to get. This accounts for the many private collections made by individuals.

Much of the material accumulated in the early days of the Museum could not be obtained today, for the improvement in medical science makes specimens of cholera, typhoid and diphtheria rare.

In 1909 the present building of the College was dedicated, and spacious quarters in it were provided for the Museum, but so numerous were our exhibits that we were obliged to put the "Brinton Collection" in what we call the "Museum Annex," a polite name for a portion of the basement just outside of the basement door of the Museum. This is a collection of plaster models of deformities of the limbs brought together by Dr. John H. Brinton, a physician who served as a member of the Mütter Museum Committee for nearly twenty-nine years. Requests are often made to see some of the types of deformities represented by the collection, but we are always apologetic when we take visitors to see them. We are not proud of their location in the building but there is no space in the Museum proper, to accommodate the three large sections that house the exhibits.

Doctor Brinton also augmented the Mütter Collection of fractures by numerous donations.

Although complete records of the activities of the Museum from 1883 to 1900 are not available, its continued growth is made evident by the fact that the first complete catalogue of its contents, compiled by Dr. Guy Hinsdale, who succeeded Doctor Bache as curator in 1883, consisted of three large typewritten volumes.

In 1915 the rail cases around the balcony were purchased, and a few years later the specimens of injuries from World War 1 were mounted and deposited in them. These were presented to the College by the U. S. Base Hospital Unit #10.

At this time, also, the Museum received from Dr. John H. Arnett various interesting appliances and apparatus used in paralysis and stiff joints during war demobilization work.

Dr. Chevalier Jackson having removed hundreds of foreign bodies from the lungs of his patients by the expert use of the bronchoscope, desired to present the collection of items he had accumulated to the Museum. In 1929 he supplied the exhibition cases and the material was assembled. It is

an awesome exhibit, not only because of its size and the skill required of the physician to remove the objects, but because of the ability of the patients to have swallowed some of them.

The Philadelphia Award to Doctor Jackson was also presented to the Museum with a case suitable for its display presented by an unknown donor.

In 1925 the upright glass cases in which the skeletons are kept, were purchased. They were planned by Dr. Milton J. Greenman, who was then a member of the Museum Committee. They are beautiful cases, almost dust-proof, and add much to the appearance of the Museum and to the effectiveness of the display.

The following year a card catalogue of the Museum material was begun and completed in 1929. This was a real necessity in order to locate pathological material on short notice, since the catalogue compiled by Dr. Guy Hinsdale was more of an accession catalogue. One was always able to find the material desired in it, but it took some time to do so.

In 1939, the Matthew H. Cryer Anatomical Collection, representing rare dental and sinus abnormalities, was presented by Mrs. Martha G. Cryer and was the last large donation of anatomical material received by the Museum.

The last pathological items to be donated were received in 1941, when that genial gentleman Dr. Elliston J. Morris walked into the Museum one fine April morning and handed me his gall bladder and appendix.

A resolution was adopted on December 2, 1874 "that the curator be instructed to receive and preserve in a suitable case such instruments as may be presented to the College." The curators have most assuredly followed these instructions during the years, and the present curator is still doing it. During the past few years the growth of the Museum has been measured principally by the addition of medical instruments, some of which are rare while others derive interest from the eminence of their former possessors.

Although the Museum now numbers over 7300 specimens, we sometimes bewail the fact that no new anatomical or pathological material is received, but if it were, we would be at a loss to know where to put it. Perhaps, like the old-fashioned Thanksgiving table, room could always be found for one more. At any rate, let us generously hope that the Museum will make the growth in the next century that it did in almost a century past, and as for space—well, after all, none of *us* will be around and someone else will have to worry about it.

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# Transactions of the Sections

## SECTION ON GENERAL MEDICINE

*January 28, 1946*

Hydropneumothorax: Comparative Speed of Fluid Absorption of Two Sides of the Chest. Robert Charr, M.D. (Commentator: Charles C. Wolferth, M.D.) *Abstract 1, below.*

Non-nephritic Uremia: the Renal Effects of Shock. Virgil H. Moon, M.D. (Commentator: Charles L. Brown, M.D.) *Abstract 2, below.*

The Mechanism of Recovery following Treatment with Penicillin. Robert A. Moore,* M.D. *To be published in a subsequent issue.*

*February 25, 1946*

Fat Metabolism and Ketone Body Formation as Shown by Heavy Carbon. Grace Medes,* Ph.D., and Sidney Weinhouse,* Ph.D. (Commentator: Samuel Gurin,* Ph.D.) *Abstract 3, below.*

Malignant Exophthalmos. Karl E. Paschkis, M.D., A. Cantarow, M.D., and A. Rakoff, M.D. (Commentator: Edward Rose, M.D.) *Abstract 4, below.*

Transitory Pulmonary Infiltrations (Loeffler's Syndrome) in Man and Rabbit. Peter A. Herbut, M.D., and Frank R. Kinsey,* M.D. (Commentator: Paul C. Swenson, M.D.) *Abstract 5, below.*

Recent Advances in Peripheral Vascular Disease. Joseph C. Doane, M.D. (Commentator: Ralph Goldsmith, M.D.) *Abstract 6, below.*

## SECTION ON OPHTHALMOLOGY[1]

*January 17, 1946*[2]

Physiological and Technical Fundamentals of Stereoscopic Fluoroscopy Especially Adapted for the Removal of Foreign Bodies. Carlos Santos,* M.D.

*February 21, 1946*

Fluorescent Colors in Tangent Screen Examination. Jacob B. Feldman,* M.D., and Harold J. Abrahams,* Ph.D.

Complete Unilateral Ophthalmoplegia Due to Primary Carcinoma of the Sphenoid Sinus (Orbital Apex-Sphenoid Fissure Syndrome): Case Report. I. S. Tassman, M.D. (Commentator: Benjamin H. Shuster, M.D.)

Tendon Transplants for Paralysis of the External Rectus Muscle: Moving-picture Demonstration. Edmund B. Spaeth, M.D.

## SECTION ON OTOLARYNGOLOGY[3]

*February 20, 1946*

Observations on the Medical Casualties of the Atomic Bomb. Austin T. Smith, M.D.

Comments on the Distribution of Certified Otologists in Pennsylvania. Douglas Macfarlan, M.D.

Progress of the Surgical Treatment of Deafness. Edward H. Campbell, M.D.

The Use of Products of Human Plasma Fractionation in Otolaryngology. Harry P. Schenck, M.D.

## Abstracts

### *Abstract 1*

Hydropneumothorax: Comparative Speed of Fluid Absorption of Two Sides of the Chest. Robert Charr, M.D.

Hydrothorax in congestive heart disease and its preponderance of right over left side is recognized. When it is bilateral, the amount is usually greater on the right side. The physiologic mechanism involved is not fully understood (1). When the hydrothorax disappears, it usually disappears first on the left side. It may partly be due to the effusion being smaller on the left side. A question

* By invitation.

[1] The transactions of this Section are customarily abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

[2] Joint meeting with the Philadelphia Roentgen Ray Society.

[3] The transactions of this Section are customarily abstracted in the *Archives of Otolaryngology*.

was raised whether a difference in the speed of fluid absorption of two sides of the chest, if present, might not be a factor. With this view in mind, the present study was made.

The series consisted of 40 patients with arrested pulmonary tuberculosis under artificial pneumothorax. In twenty the hydropneumothorax was on the right and in the rest on the left side. All were followed for three to five years. Weekly fluoroscopic observations with periodic roentgenologic examinations were made to determine the comparative speed of fluid absorption of the two sides. The fluid was aspirated from each patient to note its character. Only those whose effusion closely resembled the pleural transudate in congestive heart disease were studied. Those with greatly thickened pleura were not included.

The effusion in the left sided pneumothorax was absorbed somewhat faster than that on the right. Methylene blue when injected into the left pleural cavity appeared in the urine earlier and in larger quantities than when injected into the right.

Under fluoroscopic examination, more lively passive movements of the left lung, because of the stronger cardiac impact thereon were seen. On the right the movements were sluggish. On the left there was constant agitation of the fluid, but not on the right. The fibrin bodies were more frequently seen on the left than on the right. They were tossed about the left pleural cavity by the cardiac action until they were broken up into successively smaller balls, and finally disappeared. When an eighteen gauge needle attached to a water manometer was inserted into the left lower chest fluctuations of 2 to 5 mm. synchronous with the heart actions were seen. On the right manometric fluctuations were absent.

It is recognized that readily diffusible substances of the fluid are taken up directly by the blood stream, whereas proteins and particulate matter are removed first by the lymphatic vessels. It has been shown that the motion of the lung is important for causing lymph flow, and that in the quiescent lung the lymph flows more slowly (2). The reason for the apparently speedier absorption of the fluid on the left side in this series may be due in a measure to faster lymphatic flow brought about by greater massage and passive movements exerted upon the left lung by the contractions of the left ventricle. The pulmonary circulation too may be faster on the left side because of the greater cardiac impact. This is in a measure supported by the apparent infrequency of thrombosis of the left pulmonary artery (3). In 12 cases of ante mortem thrombosis of the pulmonary artery con firmed at autopsy, in only 2 the thrombi were on the left side; in 8 they were on the right, and in 2 on both sides. Among 88 cases collected from the literature, the thrombi were in the left pulmonary artery in only 4 cases, but on the right in 41 cases and on both sides in the rest. Regarding the bilateral cases, the authors stated that the thromb on the right appeared older, suggesting that thrombosis occurred first on the right and later extended into the left lung. One may assume that faster pulmonary circulation will sooner clear the effusion.

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*Abstract 2*

Non-nephritic Uremia: the Renal Effects of Shock. Virgil H. Moon, M.D.

The pathology of secondary shock includes marked degenerative changes in parenchymatous organs. These changes are especially severe in the kidneys, often producing necrosis of the tubular epithelium (1, 2).

Shock is accompanied by renal functional deficiency, evidenced by oliguria or anuria and by progressive retention of nitrogenous wastes. The urine contains hemoglobin, albumin, casts and debris from disintegrated cells. If neither death nor recovery occurs soon, a state of sublethal shock may continue several days. In such cases, uremia develops and frequently is the chief cause for death (2, 3).

The occurrence of shock is not limited to trauma and the aftermath of extensive surgery. Harkins (4) listed more than 30 conditions in which shock may develop. These included burns, freezing, vascular occlusions, intestinal strangulation, heat stroke, radiation burns, sunburn, bile peritonitis, visceral perforations, the effects of various drugs and poisons, venoms, peptone, anaphylaxis, transfusion reaction if severe, metabolic intoxications, and infections of fulminating severity.

I have reported the occurrence of shock under these and other conditions and have collected evi-

dence on renal deficiency associated with many of them. Clinical cases in which sublethal shock resulted in uremic manifestations, included: surgical operations, trauma, multiple fractures, extensive burns, transfusion reactions, icterus gravis, obstructive jaundice, eclampsia, severe infections such as influenza, tularemia, reaction to arsenical therapy, irradiation sickness, heat stroke, anaphylaxis, and high altitude aviation.

The morphologic changes in the kidneys were of the same pattern, regardless of the causative condition. The characteristic histologic features were: marked degeneration, ranging to necrosis, of the epithelium of the convoluted tubules, desquamation of lining, edema, casts and debris within the lumina.

The probable relationship between the degenerative changes and the functional deficiency, is that suggested by Wearn and Richards (5). Degenerated epithelium no longer performs its function of concentrating the glomerular filtrate by selective absorption. Instead, the *entire* filtrate is resorbed into the circulation by diffusion through the degenerated lining. This lowers the volume of urine excreted and results in progressive retention of nitrogenous wastes, often culminating in the syndrome of uremia.

This form of renal disease is not new; prior to 1915, it was commonly known as acute Bright's disease, acute parenchymatous, tubular or desquamative nephritis. Renal deficiency from this cause is more common than from glomerulonephritis. If the causative condition is removed and if fatal uremia does not develop, renal function is resumed and no permanent sequelae remain.

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*Abstract 3*

**Fat Metabolism and Ketone Body Formation as Shown by Heavy Carbon.** Grace Medes, PH.D., and Sidney Weinhouse, PH.D.

Metabolic studies today are concerned largely with intermediary metabolism, for which isotopes are proving to be an especially valuable tool. Joint work at Lankenau Hospital Research Institute and Houdry Process Corporation has made use of carbon of mass 13, also spoken of as heavy carbon.

The first problem investigated was to identify a possible 2-carbon fragment derived from fatty acids which might behave as a unit in fatty acid oxidations and syntheses. $C^{13}$ was introduced into the carboxyl group of short-chained fatty acids and by its distribution in the resulting ketone bodies, formed in the presence of liver slices and homogenates, it was possible to establish which of the three current theories of ketone body formation is in accordance with the experimental findings. Since $C^{13}$ was determined to be in approximately equal positions of acetoacetic acid and $\beta$-hydroxybutyric acids found after incubation of octanoic acid with liver slices, it was concluded that fatty acids oxidize with disruption into 2-carbon units, which subsequently unite 2 by 2 to form the ketone bodies.

The exact composition of this 2-carbon unit was not clear, whether acetic acid, acetyl phosphate, or some other reactive unit. However, the same distribution of $C^{13}$ was found in the ketone bodies when acetic acid was employed as substrate, indicating that at least ready transformation to the reactive form occurs.

Since ketone bodies had not previously been isolated from kidney tissue its formation was deduced by incubation of kidney homogenates with the following substrates: (1) acetic acid containing isotopic carbon. This revealed that acetic acid is utilized, while the portion recovered after incubation had decreased in its concentration of $C^{13}$; (2) acetoacetic acid which tended to disappear; (3) isotopic acetic acid plus non-isotopic acetoacetic acid. Here again, both substrates decreased in amount. The acetoacetate recovered after incubation contained acetic acid in the carboxyl and $\beta$-positions, and must therefore have arisen from the isotopic acetic acid introduced.

Heart muscle utilized acetic acid and acetoacetic acid, but the latter was not found to be a step in the oxidation of the former, since the ketone bodies isolated after incubation did not contain isotopic carbon.

Further oxidation of acetate takes place through the Krebs cycle, since isotopic carbon introduced into acetic acid has been recovered in $\alpha$-ketoglutarate. We are working on other intermediates

in this cycle in normal conditions and some states involving pathological fat metabolism.

*Abstract 4*

MALIGNANT EXOPHTHALMOS. Karl E. Paschkis, M.D., A. Cantarow, M.D., and A. Rakoff, M.D.

Observations on five patients presenting the hyperophthalmopathic type of Graves' disease are presented. The ocular manifestations include exophthalmos, swelling of the lids, edema of the conjunctivae, with ulcers of the cornea and paresis of extrinsic ocular muscles.

It was formerly believed that the ocular manifestations are due to the excess of circulating thyroid hormone. Experimental and clinical observations have proven that such is not the case. In thyroidectomized guinea pigs exophthalmos is readily induced by treatment with pituitary extracts. In humans, exophthalmos rarely recedes and mostly increases following thyroidectomy.

There exist all transitions from classical Graves' type with severe thyrotoxicosis and ocular manifestations through cases with mild thyrotoxicosis and severe eye signs to euthyroid or even hypothyroid individuals with the ocular syndrome. Means speaks of the spectrum of Graves' disease to denote these transitions.

Mulvany has attempted to attribute the ocular manifestations in classical Graves' disease to the excess of thyroid hormone, and the syndrome of the "hyperophthalmopathic type" to the thyrotrophic pituitary hormone speaking of thyrotoxic versus thyrotrophic exophthalmos. His arguments have not convinced us and we tend to accept in agreement with Means a unitarian explanation of exophthalmos for both types of cases.

Of the five cases studied by us, two had been operated upon previously for thyrotoxicosis in other hospitals and the ocular manifestations had worsened considerably. One of the two was in a very serious condition with acute danger to his eyes. In addition to treatment with thyroid and X-ray irradiation of the pituitary a decompressing operation (Kroenlein-Naffziger) had to be performed. He recovered completely. The other postoperative case was treated with thyroid and X-ray irradiation to the pituitary with good results.

Case three had very mild thyrotoxic manifestations with severe exophthalmos and paresis of extrinsic ocular muscles. We advised against operation and she was treated with large doses of diethylstilbestrol and with X-ray irradiation to the pituitary. She was considerably improv
Case four had moderate thyrotoxic manifestatic
associated with exophthalmos and paresis
ocular muscles. We advised against thyroid
tomy. He was treated with X-ray irradiation
the thyroid which brought the thyrotoxicosis unc
control. X-ray irradiation to the pituitary gla
has so far resulted in no improvement of ocu
paresis but has apparently arrested it.

Case 5 was a hypothyroid who develop
exophthalmos and ocular paresis. Treatme
given otherwhere consisted of thyroid medicati
and X-ray to the pituitary gland and resulted
considerable improvement.

*Conclusions:* In order to avoid serious danger
the eyes it is all important to avoid thyroidecton
when ocular signs are out of proportion to thyr
toxic manifestations. Therapeutic measures ava
able for combating the ophthalmopathy a
directed toward suppression of the pituita
gland: desiccated thyroid, estrogens, X-ray irrac
ation of the pituitary gland. Decompressi
operations are reserved for emergencies.

An interesting observation made in two cas
was the slow and inadequate metabolic response
thyroid medication, both oral and intravenou
This and the metabolic response to large doses
stilbestrol observed in a third case raises the que
tion whether excessive thyrotrophic pituitary ho
mone may directly counteract (inactivate?) circ
lating thyroid hormone.

*Abstract 5*

TRANSITORY PULMONARY INFILTRATIONS (LOEF
LER'S SYNDROME) IN MAN AND RABBIT. Pet
A. Herbut, M.D., and Frank R. Kinsey, M.D.

Loeffler's syndrome is a disease characterized b
few clinical manifestations and fleeting pulmon
shadows demonstrable radiologically. A review
the numerous case reports in the literature di
closes that (1) the disease is generally considere
as an allergic response of the lungs to a variety
allergens and (2) that little is known of the path
logic changes in the lungs because such patien
usually recover. In this report we will preser
a typical case of the syndrome in man and its e
perimental production in rabbits.

The patient is a woman 33 years of age who wa
confined to a sanitarium for 8 months for wha
was thought to be pulmonary tuberculosis. The
was a history of asthma in the family and on tw
occasions she was admitted to the Jefferson ho

al with typical attacks of asthma. On each of se admissions she developed pain in the chest, fer, expectoration of small amounts of sputum at contained as many as 25% eosinophiles, lood eosinophilia to 18% and characteristic roentgnographic pulmonary shadows that disappeared vthin 2 weeks.

For the experiment we used 22 rabbits. Thirteen were sensitized to horse serum and 9 were ed as controls. Three weeks after the sensitized rbbits received their last injection a blood count, rctal temperature and roentgenogram of the cest were made on all the animals and then they wre divided into two groups. Group 1 consisted o 6 sensitized and 4 controls and group 2 of 7 sisitized and 5 controls. The former received a single intratracheal injection of 5 c.c. of horse sum and the latter repeated injections of ½ c.c. o horse serum. Roentgenograms of the chest wre made at regular intervals and each was accnpanied by a rectal temperature and blood sear. All of the 13 sensitized animals developed nnor symptoms, but no blood eosinophilia or fer, and all exhibited shadows in the lungs rliologically. Three died early but in 9 of the rnaining 10 animals the shadows cleared in from 7 o 13 days. Only 2 of the 9 control rabbits devoped pulmonic shadows and these were prodced by an empyema which resulted from a p itracheal abscess. Pathologically the lesions in the lungs consisted of congestion, edema and eosinophilic infiltration of the mucosa and submucosa of the trachea and bronchi, and in the parenchyma congestion, edema, atelectasis, emphysema, and eosinophilic pneumonia. Tracheal smears disclosed as many as 81% eosinophiles in the sensitized animals as compared with 5% in the controls. The syndrome in the rabbits was thus similar to that in man with two exceptions, namely, (1) that the pulmonic shadows were not migratory and (2) that there was no blood eosinophilia.

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*Abstract 6*

Recent Advances in Peripheral Vascular Disease. Joseph C. Doane, M.D.

Interest in the study of Peripheral Vascular Disease has greatly increased in the past few years—the general practitioner has become more vascular disease conscious, the surgeon has contributed much to this development. The anticoagulants have been found highly effective. Refrigeration now is believed to be more useful than the employment of heat in treating tissue oxygen want.

Vascular tonus is a factor of great importance in the prognosis and treatment of tissue ischemia and asphyxia. The presence or absence of hypertonus can be discovered by central or peripheral sympathetic blocking and the use of a skin temperature apparatus or by observation of the changes in the temperature of the part after producing a systemic pyrexia by the use of a foreign protein intravenously.

Thrombophlebitis is a deadly post-operative complication. It occurs oftener in vaso-spastics than in those of low vascular tone. Femoral ligation before a major operation in some cases, heparinization both before and after operation, and femoral ligation, and the use of heparin after this condition has developed are advised.

Deproteinated pancreatic extract rarely brings complete relief in the treatment of intermittent claudication. Histamine iontophoresis and the use of intravenous hypertonic salt solution with papaverine in generous doses seem to promise more.

Heparin and dicoumarin are indispensable to the treatment of vascular disease, and the conservative treatment of major vascular occlusion by their aid has proven highly encouraging.

Refrigeration has now largely replaced heat therapy in treating Peripheral Vascular Disease. Shockless amputation of a limb by use of a refrigerating blanket is now possible.

Fluorescin is a useful diagnostic drug in evaluating blood supply to a part.

Phlebography and arteriography are employed with success in learning the location and degree of venous and arterial obstruction. An understanding liaison between the Internist and the Surgeon is life-saving in treating Peripheral Vascular Disease.

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# Studies on Infectious (Epidemic) Hepatitis and Serum Hepatitis*

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STUDIES on infectious diseases are highly stimulating to the investigator when the results give promise of controlling or eliminating epidemics or pandemics among populations throughout the world.

In the early development of methods for active immunization against epidemic or pandemic influenza, I can well remember our feeling that possibly a means was evolving of controlling the last great pandemic disease from which man, up to that point, had found no means of protection. If pandemic influenza, such as that of 1918, is related antigenically to influenza virus A, which it probably is, then the means of at least partial control are now available. But, a world war has now recently expanded another well-known disease, hepatitis, which usually occurred in small epidemics, into a world-wide disease, presenting thus again an additional pandemic disease and the problems of its control. It would appear probable that, given the proper environmental or genetic conditions, other viruses and bacteria may initiate additional pandemic infections in the future.

These 2 pandemic diseases, influenza and hepatitis, are of interest, not alone as a result of the recent efforts aimed toward their control, but also owing to the contrast in their pattern as related to war. Whereas influenza, as a result of the experience of 1918, has popularly been associated with war, apparently it has rarely occurred as a war disease. On the contrary, hepatitis in its largest epidemics appears to have been closely associated with wars, such as the Civil War, in certain theatres of the first World War, and now recently as a pandemic in World War II.

The reasons for this association have become quite clear as studies of pandemic hepatitis have progressed during the war in various parts of the world. Some of the studies to be reviewed here bear directly upon this question.

It is clearly shown in Table 1 that, at the beginning of the war and in contrast to the other diseases mentioned, venereal diseases and malaria —which were widespread but not of an epidemic or pandemic nature—there was little or nothing known of the etiology, mode of transmission, treatment, or prevention of hepatitis at the time World War II started.

A curious combination of circumstances added a second disease, homologous serum hepatitis, both as a prologue and curtain, at the beginning and end of the war, to the series of epidemic curves of infectious hepatitis which occurred throughout the war period. I am referring here only to the war period during which the United States was actively at war. While it was suspected early in the war, on clinical grounds, that infectious hepatitis and homologous serum hepatitis might be etiologically

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different, it was not until the last months of the war that conclusive evidence, to be outlined later, was obtained of antigenic differences between the virus agents responsible for these two types of hepatitis. Until such antigenic differences were demonstrated by studies on cross-immunity, there were few distinguishing points to be found, particularly in view of the similarity in signs and symptoms and the identical pathological findings in the liver, whether from biopsy or from autopsy.

The fact remains that tens of thousands of cases of serum hepatitis occurred in 1942 as a result of injections of yellow fever vaccine. This vaccine apparently was contaminated with a hepatitis agent by the small amount of pooled serum added as a colloid buffer to the active yellow fever virus vaccine. The epidemic peaks of hepatitis occurring each fall and early winter thereafter in the armed services, were in general distinct from the

TABLE 1

THE PROBLEM OF HEPATITIS

| Problems | Hepatitis | Malaria | Venereal Disease |
|---|---|---|---|
| Causative agent.... | Unknown | Known | Known |
| Natural route of transmission..... | Unknown | Known | Known |
| Methods of control.. | — | + | + |
| Specific treatment... | — | + | + |

serum hepatitis until, with rising battle casualties and the use of whole blood and pooled plasma transfusions, again a high incidence of serum hepatitis superimposed its curve upon an already elevated curve of incidence of infectious (epidemic) hepatitis.

It is at least of interest to the speaker to reflect upon the chain of chance which drew together the essential outline of the investigations which our group of workers have conducted in the broad field of these 2 virus infections of the liver. Perhaps the most crucial links in this chain were; first, a chance visit with Dr. Francis D. W. Lukens, in the fall of 1942, during his own severe attack of jaundice, in which a fortuitous question revealed that about 75 days preceding his illness he had received an intravenous injection of pooled convalescent mumps plasma from a source that might well have been contaminated with the serum hepatitis virus. This consideration brought clearly into focus the possible danger of hepatitis inherent in the parenterally injected plasma or blood we were using in the study of measles and mumps. Fortunately, we had preserved a considerable amount of this plasma which subsequently was shown to contain the infecting virus agent. Second, a telephone call from Dr. Charles L. Brown, concerning an epidemic of hepatitis just beginning in a boys' and girls' summer camp close to his own vacation spot in the Pocono Mountains. Third, as a result of the exigencies of war, we had collected together, a group of conscientious objectors who, as volunteers, were immediately available for study of the materials collected from the summer camp. Fourth, the fortunate opportunity afforded our group by the study of the gamma globulin fraction of pooled plasma, separated by the method of Dr. Edwin J. Cohn. We had been using this material previously in studies on measles and mumps.

More links to the chain are required than those which chance alone supplies. Not the least of these is the personnel. In particular, without Dr. John R. Neefe, Dr. Sydney S. Gellis and Dr. John Reinhold, little progress in these studies could have been made. Major James Baty provided valuable assistance in studies involving methods of water disinfection. We were indebted to the continuous encouragement and, at times, assistance of Dr. Francis Lukens and Dr. T. Grier Miller, and for the helpful advice and efforts at animal passage and cultivation in tissue culture of the viruses, to Drs. Werner and Gertrude Henle and to Dr. T. N. Harris. Also, Dr. Leslie A. Chambers has conducted valuable studies on the electrophoretic pattern of the serum in hepatitis. Dr. John Farquhar also aided in the conduct of certain studies.

Studies of other workers during the war have helped to clarify, in part, some of the unknown factors outlined in the first table, particularly as related to etiology and mode of transmission. Members of the Hepatitis Study Group in the Army Epidemiological Board, with whom we also worked, Drs. Paul and Havens, and Dr. Francis; Dr. Oliphant of the National Institute of Health; and the English workers, Van Rooyen, MacCallum, Findlay, Cameron, Bradley and others, were actively and productively engaged in this field. Owing to a lack of time, I shall only mention briefly phases of their work as they touch certain aspects of our own studies.

I propose, therefore, to select from our studies for a brief survey, three items which we believe

have a significance, not only in the present study of hepatitis in World War II, but also in the general field of virus diseases.

*First:* The transmission of the virus agent of infectious (epidemic) hepatitis by fecally-contaminated water under natural conditions, and the lack of effect of certain methods of chlorination in disinfecting such water.

*Second:* The development of a highly effective means of control of the spread of infectious (epidemic) hepatitis and the relation of such means of control to homologous serum hepatitis.

*Third:* The development of conclusive evidence of antigenic differences between the virus agent obtained from infectious (epidemic) hepatitis and the virus agent obtained from serum hepatitis.

It is of interest in relation to our first item, namely, the demonstration of a water-borne hepatitis virus under natural conditions, that within the period of a few weeks of each other, 3 groups of workers quite separately demonstrated the presence of infectious (epidemic) hepatitis virus in the stools of cases suffering from this disease. Drs. Havens, Ward, Drill, and Paul, Drs. MacCallum and Bradley and our group at the University of Pennsylvania, all successfully transmitted epidemic hepatitis by the oral route in the human, at that time the only known susceptible species of animal. However, previous to this demonstrated presence of the epidemic virus in the stool, we had amply demonstrated that stools from cases of homologous serum hepatitis due to the yellow fever vaccine virus agent, were not infective when administered orally or parenterally (Seitz filtrate) to human volunteers. This contrast in possible mode of transmission suggested a clear distinction between the virus agents responsible for these two types of hepatitis, and led to further accumulation of the evidence confirmatory of this distinction, to be described later.

The demonstration of the infectivity of the stool in infectious (epidemic) hepatitis was but a part of a larger investigation conducted of a summer camp epidemic of hepatitis in which 350 members of a total camp population of 572 developed the disease. In addition to data which have not previously been mentioned there are certain findings in this epidemic which deserve particular emphasis. These may be reviewed very briefly by means of Chart I, indicating the epidemic curves in the boys' and girls' sections of the camp, and a rough geographic outline of the camp (Chart II), supplemented by two photographs showing certain features of the camp indicated diagrammatically on Chart II.

By exclusion of the possible sources of the infecting agent other than water from the well in the girls' camp, and then by collecting all of the positive findings concerning the source of infection, it was possible to obtain conclusive evidence from the epidemiologic standpoint alone that contamination of the girls' well was responsible for the epidemic.

The possible sources which could be excluded may be summarized briefly as follows:

1. The same milk was also delivered to other neighboring camps which suffered no hepatitis.

2. The food was prepared and eaten separately by the two camps, with the exception that some of the supplies and pastries were regularly transferred from the boys' into the girls' camp, whereas the epidemic started in the girls' camp.

3. Common bathing in the lake could be excluded inasmuch as many of the children, particularly of the younger groups in both camps, did not bathe in the lake and yet developed the disease at the same time as those who did. About 42 young adults from the farmhouse, many of whom bathed in the lake, escaped the hepatitis entirely.

4. Direct contact infection could be excluded in view of the fact that large numbers of the smaller boys who developed hepatitis early in the epidemic, had had no contact with the girls. Of the 42 young adults mentioned who had close contact with the girls, none developed hepatitis. Nasopharyngeal secretions obtained preceding and during all stages of hepatitis were not infective when administered to human volunteers. Also, a majority of the children who developed hepatitis contracted the disease after they had been evacuated to their homes. Despite the fact that large numbers of these cases exposed many brothers, sisters and other young relatives at home, only five contact cases occurred. Under such circumstances, this explosive outbreak causing hepatitis in approximately two-thirds of the campers could not possibly be explained by personal contact.

5. Flies could not have acted as passive carriers of the agent since they had no access to stools. A watery extract from large numbers of flies collected in fly traps produced no hepatitis in human volunteers to whom the extract was administered

orally, and the epidemic curve indicated a source of infection which was necessarily more massive than could have been accounted for by flies. Flies also had access to the 42 young adults who lived in the immediately adjacent farmhouse, mixed with campers, and yet escaped hepatitis.

6. Most of the reasons listed in the preceding paragraph also exclude biting insects, such as mosquitoes and flies. In addition, the infecting agent has been transmitted to volunteers with difficulty by parenteral injection of blood from

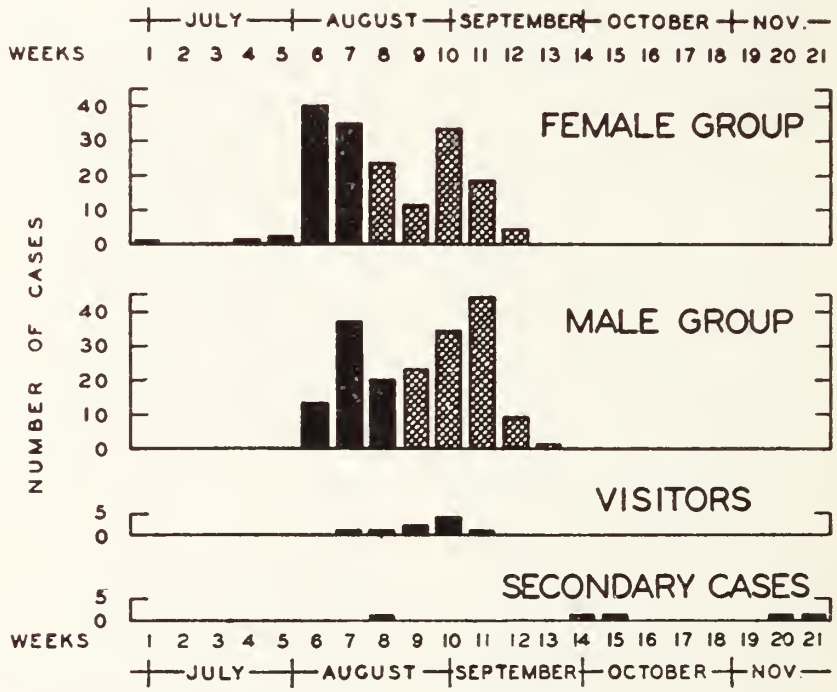


CHART I. WEEKLY INCIDENCE OF HEPATITIS

The black columns (Male and Female Groups) represent the weekly number of cases occurring at the cam while the cross-hatched columns represent the weekly number of cases occurring at home, after the closing of ea camp.

cases of the disease. Certainly this massive outbreak did not develop thru the medium of biting insects.

The positive findings which pointed directly to the girls' well water were as follows:

(a) There must have been a common massive source of infection to which the girls' camp was exposed slightly earlier and more severely than the boys' camp. The severity was indicated by the higher total incidence of hepatitis in the girls' camp. The girls' well water was pumped from time to time into the boys' reservoir and thus

fulfilled the necessary criteria for a common sour of infection with the modifications of severity an time mentioned.

(b) A direct connection was established lat between one of the cesspools draining the bun house occupied by the first two cases, and tl girls' well. When water was flushed into th cesspool after the closing of camp E. coli appear in large numbers, the water developed a fec odor, and nitrogen and ammonia increased 6 10 times in amount. The sewage of an adjace

house, used later as an infirmary also drained i this cesspool.

(c) The first case was a secretary in the gi camp and the succeeding explosive outbreak, sta ing in the girls' camp, followed at an inter compatible with the incubation period of epiden hepatitis.

(d) The girls' well-water was found to be heav contaminated with E. coli.

(e) The water used by the 42 young adults i the farmhouse, none of whom contracted hepati was from another well which was not contaminat

(f) The stools of cases of hepatitis from the boys' and girls' camps were found to be highly infective when administered orally to human volunteers. The infectivity of a Seitz$_3$ filtrate of the stools indicated that the causative agent was probably a virus.

(g) One child who visited camp for only 2 hours, who ate no food, but drank water from the girls' well, developed hepatitis 37 days later.

(h) Water collected from the girls' well, approximately 5 weeks after the camp closed, and allowed to stand 1 month in the laboratory, was fed to 5 volunteers, 4 of whom developed mild illnesses associated with hepatic dysfunction after approximately 60 days. When, after recovery, these 4 volunteers were challenged with infective stools, administered orally, they remained well, while control volunteers developed hepatitis from the infective stools similarly administered.

Until the direct connection between the cesspool and the girls' well was determined, the more important evidence in favor of a water-borne hepatitis virus as the causative agent of the epidemic appeared to be the results of feeding the well-water to the volunteers. With the establishment of this direct connection, however, the epidemiologic evidence alone appeared conclusive, inasmuch as all of the necessary evidence for incriminating the well-water was then available.

In view of this finding and of other evidence confirming the fact that this virus may on occasion be water-borne, such as that which Dr. Ross Gauld obtained from one of the divisions of the 5th Army (to be published), it appeared essential

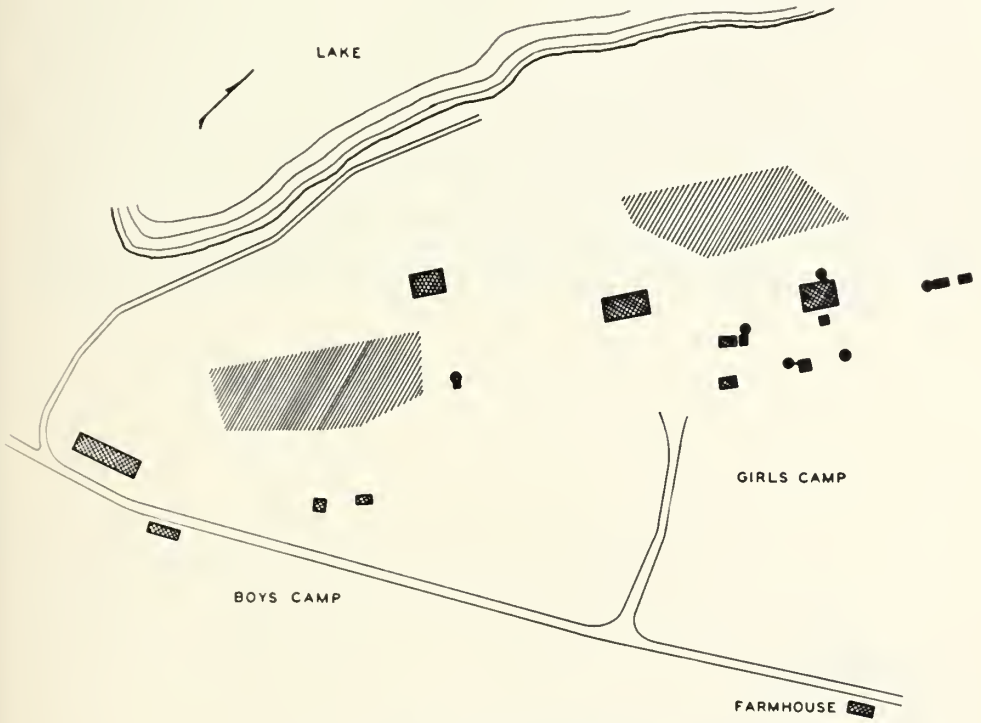


CHART II. DIAGRAM OF THE BOYS' AND GIRLS' CAMP

The boys' dining hall and kitchen are shown as the large building farthest to the left. The large shaded areas indicate the group of bunkhouses or cabins in the respective camps (see Photograph II). The cesspools surrounding the girls' well are shown as round black dots, while the well is the black square directly toward the lake from the girls' reservoir (the black dot, unattached). The black dot furthest to the left is the cesspool draining the bunkhouse and infirmary where the first cases were housed. This cesspool was 150 feet from the girls' well. The farmhouse which housed 42 young adults is indicated in the lower right corner. Photograph I shows certain features of the camp which are indicated diagrammatically on this chart.

PHOTOGRAPH I. The road dividing roughly the two camps is shown on the far right. Little of the girls' camp is shown in the photograph with the exception of the cabin and infirmary where the first cases occurred (shown between the fork in the road) and the girls' water reservoir, the last building (round tower) on the right. The boys' camp and the lake beyond are on the left side of the photograph.

PHOTOGRAPH II. THE BUNKHOUSES OR CABINS IN THE GIRLS' CAMP

to determine the value of the ordinary methods of chlorination used by the U. S. Army (Lister bag technique) for inactivating the epidemic hepatitis virus in drinking water. To summarize work already published and carried out, for the most part by Dr. John Neefe and Major James Baty, it was found that this method of chlorination, which aims to provide a chlorine residual of 1 p.p.m. in the drinking water, was inadequate for inactivation of the hepatitis virus in heavily contaminated water. However, further modification of the technique in which coagulation and filtration were

It must be pointed out that a chlorine residual of 1 p.p.m. is considerably greater than the amount present in a city water supply, such as that of Philadelphia. The coagulation and filtration alone, although more carefully controlled in these experiments than is possible under the usual conditions obtaining in a city water supply, failed to disinfect the contaminated water. Thus, the safety of a city supply apparently depends upon the amount of chlorine necessary to inactivate the hepatitis virus following coagulation and filtration. This amount may be considerably greater than

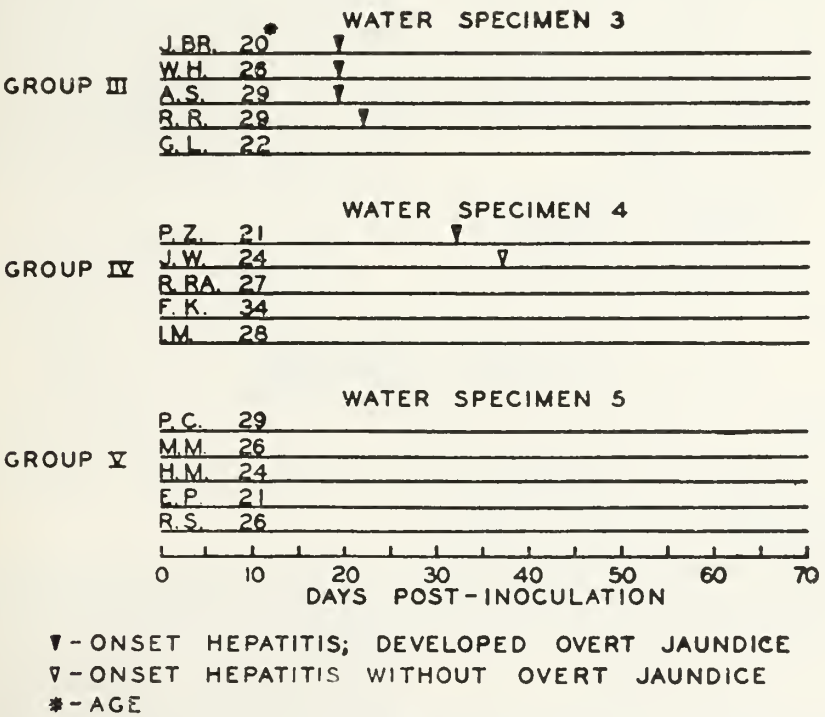


Chart III. Incidence and Time of Onset of Hepatitis in Volunteers after Ingestion of Water Specimens

used, previous to chlorination (1 p.p.m.), appeared successful, in that volunteers who drank the water, first contaminated and then treated by this means, failed to develop hepatitis. Coagulation and filtration alone did not inactivate the virus. Control volunteers who ingested similarly contaminated water, which was untreated, developed the disease. A similar experiment carried out with additional groups of volunteers confirmed the value of this technique of disinfecting drinking-water. Chart III illustrates the results of such an experiment.

that ordinarily used, in view of the failure of the Lister bag technique to disinfect the water used in these experiments.

The conclusions of this first portion of our studies may be outlined as follows:

1. The virus of epidemic or infectious hepatitis is at times water-borne and may infect by this route.

We believe this is the first time a virus has been shown conclusively to infect through drinking water under natural conditions.

2. The difficulty of disinfecting contaminated

water containing the hepatitis virus has posed new problems of the greatest importance in the broad field of water sanitation. Obviously, these problems may not be limited to a single virus infection.

The second item I have selected will be outlined very briefly. It is reviewed here for the purpose of pointing out certain important problems which have arisen and which remain to be studied.

*Gamma Globulin—Fraction II*—obtained from the large pools of American Red Cross plasma, and fractionated by the method of Cohn—has been very effective in passively protecting against infectious (epidemic) hepatitis. Table 2 indicates some of the experimental findings both in this country and in the Mediterranean Theatre of Operations. This material, injected intramuscularly in doses of approximately .06 ml. per lb. was highly successful, not only in protecting the exposed susceptible from hepatitis, but also, when given very late in the incubation period, was effective in attenuating the disease.

TABLE 2

PROTECTIVE VALUE OF HUMAN IMMUNE SERUM GLOBULIN (GAMMA GLOBULIN) IN INFECTIOUS (EPIDEMIC) HEPATITIS

| Epidemic | Group | | | | Ratio* |
|---|---|---|---|---|---|
| | Control | | Globulin | | |
| | No. | Jaundice | No. | Jaundice | |
| | | % | | % | |
| Pennsylvania (Stokes & Neefe)..... | 491 | 51 | 54 | 5.6 | 9.8 to 1 |
| MTO (Gellis, Stokes, et al.)..... | 10,326 | 3.2 | 1732 | 0.5 | 6.4 to 1 |

In another epidemic in MTO, incidence of jaundice in control and globulin groups was as 25 to 1 (Gellis, Stokes, et al.). In an epidemic in Connecticut studied by Paul and Havens, similar protective effect observed in group receiving globulin.

* Ratio—incidence of jaundice cases in control group to incidence in globulin group.

Throughout World War II, the great body of medical opinion has linked together infectious (epidemic) hepatitis and serum hepatitis as a single disease entity. It is a natural endeavor throughout the field of medicine, to simplify etiologic factors as far as possible. Too frequently, in virus diseases, however, attempts at simplifying the causative factors have obscured their true nature.

The effect of gamma globulin in protecting against epidemic hepatitis suggested its possible usefulness in serum hepatitis. Just as the infectivity of the stools has indicated a difference between these two types of hepatitis, so also the results of the use of gamma globulin have served to differentiate them. Table 3 outlines controlled studies at two widely-separated army general hospitals in the zone of the interior, in which alternate battle casualties, who had received blood or plasma or both at the time of injury in the various theatres of war, were injected with 10 ml. of gamma globulin in one dose or in two doses, one month apart. There was no question but that a virus, or viruses, in the blood products were responsible for the serum hepatitis, inasmuch as casualties from the same theatres who did not receive transfusions of such products, with but few exceptions, escaped the disease. It will be noted that the general hospital, at which 2 doses of gamma globulin were injected at an interval of 1 month, had a far higher incidence of hepatitis in the control group and a far greater effect of the gamma globulin in the injected group than was found in the first hospital at which a single dose of 10 ml. was injected. In fact, there is no significant difference in the incidence of hepatitis in the injected and control groups in the first hospital. Chart IV, however, indicates that, while the incidence was similar in the two groups in this hospital, the average incubation period of those casualties receiving the single injection of globulin was lengthened. The chance statistically, that such lengthening of the incubation period is *not* significant, is approximately one in four hundred.

TABLE 3

EFFECT OF ONE AND TWO DOSES OF GAMMA GLOBULIN IN SERUM HEPATITIS

| Army General Hospital | No. of Doses of Gamma Globulin | No. of Controls | No. Injected with Gamma Globulin | Hepatitis | |
|---|---|---|---|---|---|
| | | | | Control Group | Test Group |
| #1 | 1 | 2374 | 2406 | 23 | 29 |
| #2 | 2 | 384 | 384 | 34 | 5 |

Inasmuch as both of these studies appear to

indicate the presence of antibodies against serum hepatitis virus in the gamma globulin used, an interesting problem is propounded by the difference in the effect of the single and double injections of gamma globulin.

There appear to be two principle lines along which further progress toward a solution of this problem lies.

First, the reason for the difference between the results in the two studies may lie only in the difference in the amount of antibody used. It is possible that had 20 ml. of gamma globulin been injected in a single dose at the first hospital, rather than 10 ml., its protective effect might have been as striking as at the second hospital, which used 2 injections of 10 ml. each, at a one-month interval. This is readily susceptible to further investigation.

Second, the difference may have been induced at the second injection by an attack of antibodies on the virus antigen at a point in the incubation period during which it was more vulnerable, possibly as a result of its extracellular position in the blood plasma. The earlier incubation phase may be a less vulnerable period for the virus.

These two lines of thought postulate a certain general constancy of antibody titer in the gamma globulin used. Although antibodies to other virus diseases occur in remarkably constant amounts in the gamma globulin obtained from the different large pools of plasma, and their levels are maintained for long periods of time at ordinary ice-box temperature, such constancy and longevity may not obtain in the antibodies against serum hepatitis. The difference in the results at the two hospitals could be explained, therefore, on the basis of differences in antibody level in various batches of gamma globulin, whether in respect to the source, the age, or the method of preservation of the material. An explanation based on these factors, nevertheless, appears improbable.

It has not been unusual in another virus disease, epidemic parotitis, which has a comparatively long incubation period, to find that convalescent serum will protect exposed susceptibles in a few cases, fail to protect in many cases, but, in a certain number, will apparently greatly prolong the incubation period. In this disease, the simplest explanation of these findings would be quantitative difference in the amount of protective antibody as related to quantitative differences in the amount of virus antigen. Under these conditions, it is possible that if not quite all of the virus antigen is neutralized by antibody, it may require a longer interval until the quantity of virus particles has reached a stage at which they can bring about a typical attack of the disease. Thus, the incubation period may be considerably lengthened.

This rather simple quantitative relationship would appear to be the most satisfactory explanation, were it not for the fact that a single experi-

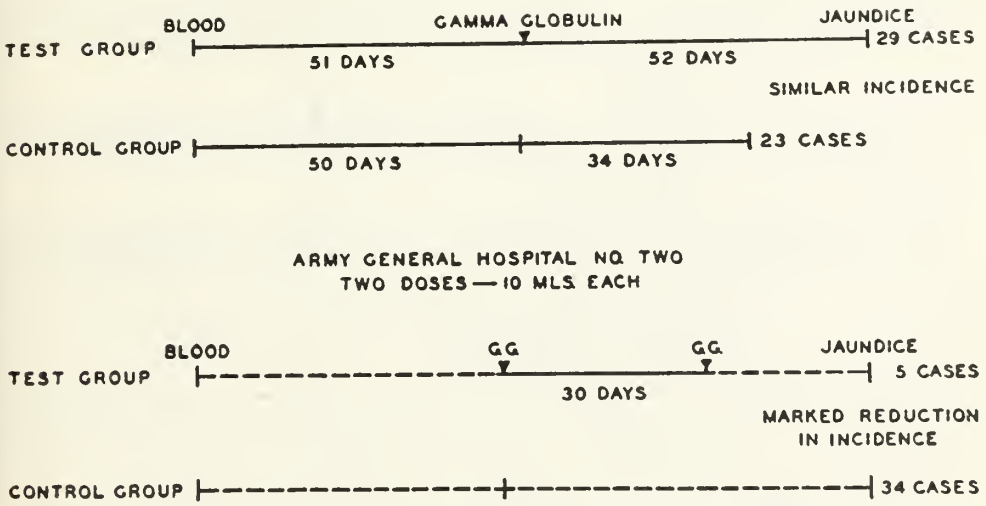


Chart IV. Effect of One and Two Doses of Gamma Globulin in Serum Hepatitis
Army General Hospital No. One. One dose—10 mls.

mental injection, in volunteers, of a mixture of 2 ml. of infective plasma of serum hepatitis with 1 ml. of gamma globulin, caused serum hepatitis in 3 of 5 men injected parenterally, with the usual long incubation period. This apparent lack of antibody effect in this single neutralization study may be explained in a number of ways. These possible explanations are not within the scope of this presentation. However, it may be added that this single study does not indicate an absence of distinct virus agents, one of which appears to be the main etiologic factor in infectious (epidemic) hepatitis, and the other, at least one of the main etiologic factors in serum hepatitis. Oliphant, as the result of a small group of cross-immunity experiments, believed that the two diseases were antigenically similar. His virus of infectious (epidemic) hepatitis, although obtained from Italy, may actually have been a virus of serum hepatitis, inasmuch as the incubation period of this agent was

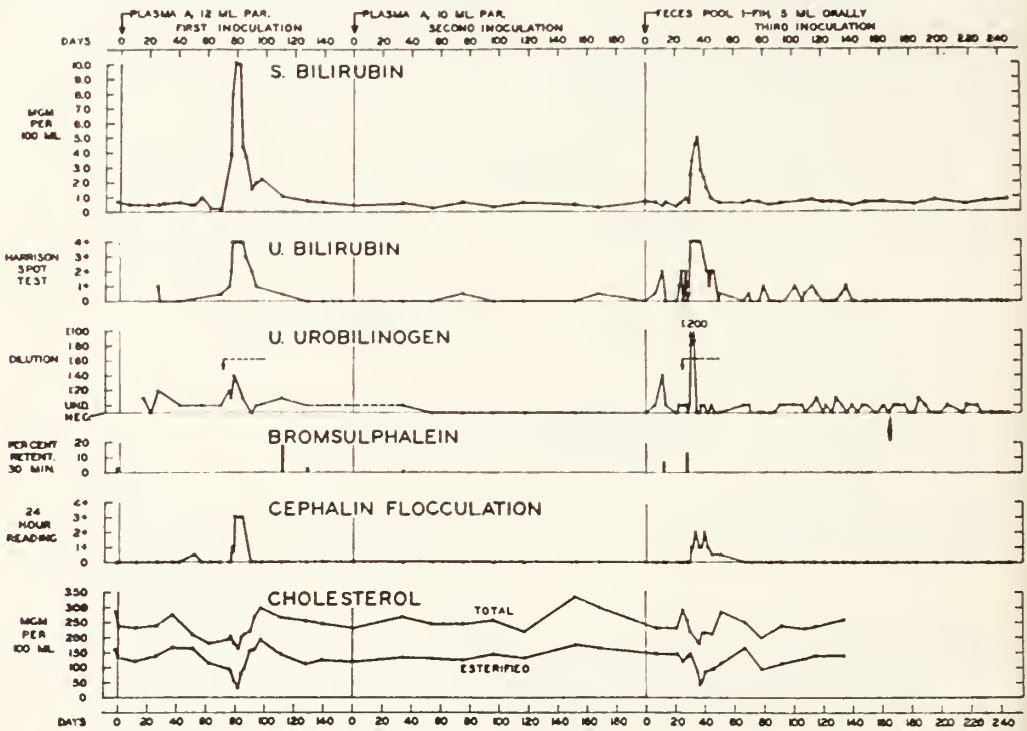


Chart V. Indicates the Method of Conducting Studies on Cross Immunity

In this individual (R.R.M.) the serum hepatitis agent was injected first. At a suitable interval the same agent was again injected parenterally. Again after an interval the agent of epidemic hepatitis was inoculated orally. Homologous immunity was present while heterologous immunity was absent. In additional experiments the route of inoculation was found not to be responsible for the lack of heterologous immunity.

Plasma A = pooled convalescent mumps plasma (Fort Bragg). FIH = feces infectious hepatitis.

antibody against the serum hepatitis virus in the usual batches of gamma globulin used in the General Hospitals mentioned. In fact, the studies outlined would strongly suggest that antibodies against the serum hepatitis virus agent are present in the gamma globulin used.

The third item I have selected has been mentioned in the discussions of the first two, and has become clearer during the progress of the studies, namely, the separation of at least two antigenically-

approximately 75 days. The work at New Haven of Havens and Paul has been closely similar to our work in Philadelphia, suggesting distinct antigenic differences in the viruses studied.

Chart V indicates our general method of approach to this problem. In one set of experiments, the serum hepatitis virus was inoculated first and, for determination of cross-immunity, the infectious hepatitis virus (summer camp agent) was later inoculated. In the second set of exper

ments, the infectious hepatitis virus (summer camp agent) was first inoculated, with a subsequent testing of cross-immunity by inoculation of the serum hepatitis virus. With both viruses, homologous immunity was first determined in the volunteers, and found to be present, before the heterologous virus was inoculated in testing for cross-immunity. In testing for homologous immunity, groups of controls were inoculated at the same time. In this way, it was possible to confirm the presence of active virus in the inoculum used for both the test and control groups. These tests indicated conclusively that these two viruses differed antigenically.

The final results, together with other differences noted between the two viruses or the diseases caused by these viruses, are indicated in Table 4. A small amount of evidence has been obtained that

TABLE 4

INFECTIOUS (EPIDEMIC) HEPATITIS AND HOMOLOGOUS SERUM HEPATITIS COMPARISON

| Observation | Infectious Hepatitis | Serum Hepatitis |
|---|---|---|
| 1. Fever associated with onset | Usually exceeds 100°F. | Seldom exceeds 100°F. |
| 2. Usual interval from exposure to jaundice. | 20–40 days | 60–120 days |
| 3. Secondary cases not related to injection of blood products | Common | Uncommon |
| 4. Human biological materials known to contain causative agent | Feces and blood | Blood |
| 5. Age susceptibility | Uncommon after 40 | Apparently common after 40 |
| 6. Oral administration of infective serum | + | − |
| 7. Homologous immunity | + | + |
| 8. Heterologous immunity | − | − |

the infectious (epidemic) hepatitis virus (summer camp) obtained in the United States is antigenically similar to the infectious (epidemic) hepatitis virus obtained by Havens and Paul in the Mediterranean Theatre of Operations, inasmuch as in one experiment a cross-immunity between the 2 agents apparently was present.

With this new knowledge, we may now return to Table 1 and to the etiology, mode of transmission, prevention and treatment of hepatitis as the war ends. In the studies outlined, the following points apparently have been demonstrated:

1. Hepatitis may be caused by at least two virus agents which antigenically are quite distinct.

2. The mode of transmission of infectious (epidemic) hepatitis appears to be by direct or indirect fecal contamination. We have demonstrated a possible water-borne route, but it also appears possible that food, personal contact, fomites, or possibly flies as passive carriers of filth, may be responsible for its transmission. The pandemic spread of the disease in war-time may be considered as evidence of increase in filth and lack of sanitation on a world-wide scale.

The evidence of a water-borne spread in more than one sharp outbreak, and the ineffectiveness of certain methods of disinfection for inactivating the virus, open entirely new problems in the field of water sanitation.

The mode of transmission and epidemiology of serum hepatitis are far more difficult to explain. It is probably far less frequent than the epidemic disease, but here again the widespread use of contaminated biological products during war-time may expand it rapidly into a pandemic disease. Biting insects could well explain the transmission of certain cases.

3. Owing to the fact that four epidemics of infectious hepatitis in widely-separated areas have yielded to passive immunization by means of different batches of gamma globulin, a means of control of spreading epidemics of this disease apparently is now available. Pure supplies of water and elimination of filth may be of great importance.

In contrast to epidemic hepatitis there is as yet no method available for the prevention of serum hepatitis. If future studies confirm those reported here, gamma globulin or immune bodies in sufficient amounts, of a suitable type, and at the proper time, may prove to be of value. Tests for contamination and for susceptibility, and the

discovery of susceptible animals would greatly assist in such studies.

Gamma globulin for treatment in a small series of cases has been of little, if any, value, nor have any therapeutic procedures beyond rest, high protein diet, and intravenous plasma.

Finally, it should be pointed out that while the urgency of war, the availability of human volunteers, and the appropriation of funds ordinarily unavailable in peace-time, have greatly accelerated the obtaining of data in these infectious diseases, nevertheless essential progress depends to a greater extent upon ideas developed in peace-time than upon action developed in war-time.

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# Recent Studies in Arsenical Chemotherapy[1]

*By* HARRY EAGLE[2]

NO ONE will question the statement that the antibiotics represent the most striking chemotherapeutic advance in our time. At least to date, however, compounds such as penicillin and streptomycin are few in number; and striking as their effect may be on susceptible organisms, as yet but few infections other than those caused by bacteria have been shown to be amenable to treatment. Even in the case of early syphilis, present information suggests that penicillin alone and in the schedules heretofore used may be inadequate. At least for the present, and perhaps for a long time to come, we will continue to use arsenicals and antimonials in the chemotherapy of a wide variety of diseases.

The present communication will deal with three aspects of arsenical chemotherapy with which our laboratory has been concerned over the past few years: the treatment of sleeping sickness, the treatment of syphilis, and the use of BAL for the treatment of arsenic poisoning. Of necessity I cannot present a well-rounded summary of these problems, but will discuss only those specific and limited aspects which we have been studying. The term "we" is not used editorially, but applies to a group of collaborators. I specifically wish to mention Drs. G. O. Doak and H. G. Steinman on the chemical side, and Dr. R. B. Hogan, Dr. H. J. Magnuson and Mr. Ralph Fleischman on the biological side.

## Trypanosomiasis

Over a period of years we had been preparing a large series of arsenicals, which were studied with a view to their possible utility in the treatment of syphilis. At the same time, those compounds were assayed against a variety of pathogenic protozoa, including trypanosomes. After synthesizing several hundred compounds along carefully planned lines (1)(2)(3), the compound which proved to be by far the best trypanocidal agent in the series came as a complete surprise. As a rule, acid-substituted phenylarsenoxides are relatively inactive (4)(5), because the ionized acidic substituent usually prevents that combination of the arsenical with the cell which is an essential preliminary to parasiticidal action (6). Paradoxically, however, the p-arsenosophenylbutyric acid compound was highly active against a laboratory strain of T. equiperdum (7). Some of the material was then sent to Dr. Scott at Manchester, England, and to Dr. van Hoof at Leopoldville, Belgian Congo, to be tested in laboratory animals against the species of trypanosome pathogenic for man, T. gambiense and T. rhodesiense, and which were not available in this country. When the compound proved as active against these (8)(9) as it was against T. equiperdum, combining a high degree of efficacy with a wide margin of safety, clinical trial was instituted. Beginning in the fall of 1944, and with the cooperation of the sleeping sickness services of Nigeria, the Gold Coast, the Firestone Plantation in Liberia, French Equatorial Africa, French West Africa, and the Belgian Congo, cases in both the early and late stages of trypanosomiasis were treated on a variety of schedules, some daily, some every other day, and some weekly, with widely varying doses, in order to establish the toxic level of the drug, the minimum curative dose and the best method of administration. In the fall of 1945 I returned to Africa and revisited these areas in order to assemble the data in the cases which had previously been treated, and to initiate new schedules in the light of that experience. The results may be briefly summarized (10) (11):

1) Cases of sleeping sickness are ordinarily diagnosed by the demonstration of the organisms in the cervical lymph nodes or in the blood. These organisms usually disappeared within ½ to 1 hour after the injection of 0.3 to 0.6 mg. per kg. of the compound.

2) In the early cases toxic reactions were minimal. The nausea and vomiting so often observed after the use of trivalent arsenicals in

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e.g. the treatment of syphilis were conspicuously uncommon. Seven patients were treated in error with 2 mg. per kg. daily for 5 to 10 days, with no untoward reaction. In the light of that experience, in one treatment center a few patients were deliberately injected at 1.5 mg. per kg., and the same dose was repeated 2 hours later. The total of 3 mg. per kg. was 7 times the average dose, and was not followed by either immediate or delayed toxic reactions.

3) An analysis of the first 319 early cases showed that African sleeping sickness in its early stages, before the central nervous system had been involved, can be cured within 1 to 2 weeks by the injection of p-arsenosophenylbutyric acid to a total of only 5 to 7 mg. per kg. (Table 1). This may be administered in two weeks by 12 to 14 injections at 0.5 mg. per kg., an average dose of 30 mgs. per injection; or treatment may be completed within one week by 7 daily injections at 1 mg. per kg.

TABLE I

*Results in Early Trypanosomiasis in Relation to Amount of Treatment with p-Arsenosophenylbutyric Acid (after Eagle (11))*

| Total treatment, mg./kg. | No. patients | Failures | | Apparent cures to date, % |
|---|---|---|---|---|
| | | No. | % | |
| <3.5 | 43 | 11 | 26 | 74 |
| 3.5–4.9 | 31 | 3 | 10 | 90 |
| 5.0–6.4 | 36 | 3 | 8 | 92 |
| >6.5 | 88 | 4 | 5 | 95 |

4) In late cases, with central nervous system involvement, p-arsenosophenylbutyric acid alone does not suffice, presumably because it does not penetrate the central nervous system in sufficient concentration. Studies are now under way to determine its efficacy when used in combination with tryparsamide and other arsonic acids.

## Syphilis

The second topic I wish to touch on this evening is the treatment of syphilis. The discovery of the therapeutic action of penicillin in this disease (12) at first seemed to render obsolete all our previous experience with arsenic and bismuth. However, more recent data (13) (14) indicate that at least in early syphilis, the results achieved with penicillin alone on any schedule of treatment yet tried are not as good as those possible to attain with arsenic and bismuth, provisional estimates indicating a relapse rate within one year in excess of fifteen per cent, this figure not including the sero-resistant cases. Under such circumstances it becomes of interest to inquire into the possibility of using penicillin and arsenicals such as mapharsen in conjunction; and we have recently completed some animal studies which are of interest in this connection (15). A group of syphilitic rabbits were given varying doses of sodium penicillin on a treatment schedule known to be grossly inefficient, i.e., injections twice daily for 4 days. On that schedule, the curative dose of penicillin was 80,000 units per kg., and 44,000 units per kg. cured only half the animals. If, simultaneous with the penicillin, the animals were given mapharsen, but in amounts so small as not to cure any of the animals if used alone, there was a striking reduction in the curative dose of penicillin. With as little as 0.15 mg. per kg. of mapharsen given daily for 4 days, the $CD_{90}$ and $CD_{50}$ doses of penicillin were significantly reduced, the latter from 44,000 to 6000; and if the dose of mapharsen was increased to 0.4 mg. per kg., in

TABLE 2

*The Synergistic Action of Penicillin and Oxophenarsine Hydrochloride ("Mapharsen") in the Treatment of Experimental (Rabbit) Syphilis (after Eagle, Magnuson & Fleischman (15))*

| Dosage of mapharsen mg./kg. | Curative dose of penicillin, units/kg. total | | Fractions of curative dose of penicillin and mapharsen effective when used in combination | | | |
|---|---|---|---|---|---|---|
| | | | $CD_{50}$ | | $CD_{90}$ | |
| | $CD_{50}$ | $CD_{90}$ | Mapharsen | Penicillin | Mapharsen | Penicillin |
| Series A. Sodium penicillin injected twice daily, at 6 hour intervals, for four days; "mapharsen" injected once daily, midway between the two injections of penicillin | | | | | | |
| 0 | 44,000 | 80,000 | 0 | 1 | 0 | 1 |
| 0.15 | 6,100 | 32,000 | $\frac{1}{4}$ | $\frac{1}{7}$ | $\frac{1}{5}$ | $\frac{2}{5}\pm$ |
| 0.4 | 800 | 4,000 | $\frac{2}{3}$ | $\frac{1}{55}$ | $\frac{1}{2}$ | $\frac{1}{20}\pm$ |
| Series B. Sodium penicillin injected five times daily, at four hour intervals, for five days; "mapharsen" injected once daily, midway between two injections of penicillin | | | | | | |
| 0 | 1,850 | 8,400 | 0 | 1 | 0 | 1 |
| 0.4 | 320 | 1,000 | $\frac{2}{3}$ | $\frac{1}{6}$ | $\frac{1}{2}$ | $\frac{1}{8}$ |

ielf still a subcurative dose, the $CD_{90}$ and $CD_{50}$ lvels of penicillin were further reduced, the latter 800 units/kg. This was 1/50th of the curative ose of penicillin when used alone, and clearly dicates a synergistic action between penicillin ad mapharsen (Table 2).

Qualitatively similar results were obtained even hen the rabbits were treated with penicillin by fairly efficient schedule, 5 injections each day, 4-hour intervals, for 4 consecutive days. On at schedule of administration, the curative dose $CD_{90}$) of penicillin alone was 8400 units/kg. his was reduced to 1000 units/kg., or 1/8th the iginal level, by the simultaneous administration subcurative doses of mapharsen (0.4 mg./kg.).

Several possible explanations may be offered r this synergistic action. It is known that even ıbcurative doses of either penicillin or mapharn kill most of the spirochetes in the infected ost, whether rabbit or man. By far the largest ortion of the treatment schedule is devoted to the adication of a relatively small number of surving organisms, either inherently more resistant present in foci relatively inaccessible to the rug. These potential survivors, altho resistant drug A, e.g. penicillin, may be normally susptible (or normally accessible) to drug B, e.g. ıapharsen. Under such circumstances, the comination of the two may effect sterilization of the ost and biologic cure. It is possible also that the w resistant organisms to the one drug which are otentially survivors are nevertheless temporarily ıjured by its action, to the degree that small and rdinarily non-curative doses of a second drug ıffice to cause their death.

Whatever the explanation, it is clear that ıapharsen and penicillin are synergistic in their ction in experimental animals; and the use of hese drugs in combination is a promising approach the more effective treatment of early syphilis. f bismuth should also prove to be synergistic ith penicillin (and there is good reason to susect that it may be), the present method of choice or the treatment of early syphilis may well be the imultaneous use of mapharsen, penicillin and ismuth. Several clinical studies are now in rogress, both in the Rapid Treatment Centers f the U. S. Public Health Service, and under the uspices of the Penicillin Panel of the National Research Council, to determine the optimum comination of these three drugs with respect to the otal dosage of each, the duration of treatment, nd the number of injections.

## BAL

The compound known as BAL (British Anti-Lewisite; 2,3-dimercaptopropanol) was developed during the war by a group of British workers for the treatment of arsenical blister gas injuries. Stocken and Thompson (16), working in Professor Peters' laboratory at Cambridge, demonstrated that when arsenic combines with keratin, and presumably other proteins as well, a major portion of the arsenic is bound to two thiol groups rather than one. They reasoned a) that the arsenic was in part bound to dithiols, rather than monothiols such as cysteine or glutathione, b) that the stability of the arsenic-tissue compound was due to the formation of a stable five-membered ring, and further, c) that this combination could be most efficiently reversed by a competing dithiol rather than by a monothiol such as cysteine or glutathione. This hypothesis was brilliantly confirmed; and BAL is one of a large group of dithiols found capable of removing arsenic from its combination with tissue proteins.

The ability of BAL to remove arsenic from cells was subsequently demonstrated in vitro (17) with protozoal suspensions, immobilized and apparently killed by arsenicals, and which are actually resuscitated when the arsenic is removed.

Thompson and Stocken (cf. (16)) had demonstrated that the injection of BAL in rats poisoned by the application of Lewisite to the intact skin was followed by a four-fold increase in the rate of urinary arsenic excretion. This suggested the possibility of using BAL, not only topically for the local decontamination and treatment of skin and eye burns, but by injection for the treatment of the systemic manifestations of arsenic poisoning as well. Our studies (17–20) have largely related to this systemic use of BAL in the treatment of arsenic and antimony poisoning. The effect of BAL on arsenic excretion was confirmed and extended in rabbits poisoned by the subcutaneous or intravenous injection of mapharsen, Lewisite or phenylarsenoxide. The administration of BAL, whether by inunction or by subcutaneous, intramuscular or intravenous injection was followed by an increase in the rate of urinary arsenic excretion, in some cases of more than 100-fold. A majority of the animals receiving otherwise lethal doses of these arsenicals could be saved by appropriate systemic treatment.

The difficulty with the use of BAL lay in its marked instability in either aqueous solution or in

propylene glycol. That difficulty was resolved with the finding that BAL formed a stable solution in peanut oil, in which it could be dissolved to any desired concentration by the addition of benzyl benzoate as a solubilizing agent. Such solutions could be sterilized in glass-sealed ampules with only slight loss in activity, were no more toxic than the aqueous solutions, and were fully as active in the treatment of experimental arsenic poisoning.

The widest margin of safety between the toxic and therapeutic levels was provided by injections repeated at 4-hour intervals. This was also the maximum period of time over which a single injection of BAL continued to promote the

TABLE 3

*Recommended schedule for administration of BAL in cases of arsenical poisoning*

(All injections at four hour intervals, intramuscular) (after Eagle (18))

| Toxic complication | Each injection | | | | Number of injections on day | | | |
|---|---|---|---|---|---|---|---|---|
| | Mg. per kg. | Body weight | | Dose, cc. of 10% solution | 1 | 2 | 3 | 4–10 |
| | | pounds | kg. | | All injections at 4-hr. intervals | | | |
| *Severe* | 3 | <120 | <55 | −1.7 | 6 | 6 | 4 | 2 daily |
| Encephalitis | | 120–155 | 55–70 | 1.9 | | | | |
| Exfoliative dermatitis | | 155–185 | 70–85 | 2.3 | | | | |
| Overdose of arsenical | | >185 | >85 | 2.4− | | | | |
| Blood dyscrasias | | | | | | | | |
| Jaundice | | | | | | | | |
| *Mild* | 2.5 | <120 | <55 | −1.4 | 4 | 4 | 2 | 1–2 daily |
| Papular dermatitis | | 120–155 | 55–70 | 1.6 | | | | |
| Fever | | 155–185 | 70–85 | 1.9 | | | | |
| "Ninth-day erythema" | | >185 | >85 | 2.0− | | | | |

urinary excretion of arsenic. It was therefore decided to use injections of BAL repeated at 4-hour intervals for the treatment of arsenic poisoning in man. It remained only to determine the maximum dose which could be administered with safety.

A significant proportion of rabbits poisoned with arsenicals had been saved by as little as 2.5 to 5 mg./kg. repeated at 4-hourly intervals. Although the maximum tolerated dose of BAL on that schedule of injections was 25 mg./kg., it was decided to study the effect of BAL in low dosage in some normal human volunteers. Injections at 2.5 and 3 mg./kg. gave no difficulty. With larger doses, however, a significant proportion of the injections were followed by subjective symptoms. In order of decreasing frequency these consisted of nausea and vomiting; headach a burning sensation in the mucous membrane sometimes accompanied by salivation, lachrym tion and pain in the teeth; tingling in the e tremities, sometimes associated with muscul aches; a sense of constriction in the chest, wit agitation and a sense of anxiety; and, as noted b Sulzberger and his associates (21), a rise in bloc pressure. These symptoms and signs were sel limited, and subsided spontaneously in 30–9 minutes. At the higher doses, however, they we sufficiently distressing to the patient to make advisable to limit the individual injection to 2 mg./kg., at which level minor reactions were o served after only 1 per cent of the injections.

Reports have been received to date (18) or total of 227 cases of various types of arsenic poiso ing treated with BAL at a dosage schedule whi we now believe can be increased. The resul strongly suggest that BAL administered prompt and in adequate dosage favorably affects the pro nosis and course of arsenic poisoning.

a) Of 55 cases of toxic encephalitis, 40 of who were convulsing or in coma, 44 recovered a 11 died, a mortality of 20 per cent. Five of t 11 deaths occurred in a small group of 9 patien in whom treatment had been delayed for 9 to hours after the onset of cerebral symptoms.

b) In 88 cases of arsenical dermatitis, includi 51 typical exfoliating cases, the administration BAL usually stopped the progression of the i flammatory reaction and accelerated the heali

process. The average time for definite improvement in the cases which responded to treatment was three days, and the average time for 75 to 90 per cent recovery was 13 days. Although 20 per cent of the cases did not respond, there is reason to suspect that this proportion may be reduced with a more intensive treatment schedule.

c) In the dosages used, BAL had no effect in 3 cases of aplastic anemia. However, in 10 of 11 cases of agranulocytosis, its administration was followed by a prompt increase in the polymorphonuclear leucocytes and total white blood cell count, which approached normal limits in 7–10 days.

d) In 5 of 14 cases of jaundice, there was symptomatic improvement after the administration of BAL, in 3 cases associated with a rapid decrease in the icteric index. Seven of the cases seemed wholly unaffected by its administration, and in 2 the effect of BAL was debatable. These findings are of interest in relation to the debatable role of arsenic in the causation of so-called post-arsenical jaundice.

e) Of 4 patients who received a massive overdose of mapharsen, 3 recovered on treatment with BAL. The fourth case, who was given 1200 mg. in a single injection, showed so favorable a symptomatic response to BAL that treatment was discontinued after he had received 3 injections of 150 mg. each. The patient developed further complications on the seventh day, and eventually died.

f) Forty-four cases of fever occurring as a complication of arsenotherapy recovered without incident. Although this complication is almost always self-limited even without treatment, the usually prompt disappearance of associated toxic symptoms suggests that BAL may have accelerated recovery.

The results outlined above were obtained with dosages of BAL which in many cases were even less than those originally recommended. There is reason to believe that those results may be significantly improved by the more intensive treatment now recommended, and outlined in Table 3.

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## Résumé

La communication actuelle est un sommaire de quelques études récentes au sujet de l'emploi des arsénicaux dans le traitement de la trypanosomiase et de la syphilis, ainsi que l'étude de la désintoxication arsénicale par le BAL.

1) l'acide p-Arsénosophénylbutyrique a donné de bons résultats dans le traitement de la trypanosomiase à son début. Les sujets pris au début de leur maladie peuvent être guéris par un traitement de 1 à 2 semaines. Ce traitement consiste en des injections quotidiennes de 1 mg. ou de 0.5 mg. par kilo de poids.

2) Le mapharsen et la pénicilline ont une action synergique dans le traitement de la syphilis expérimentale, à tel point que leur emploi combiné donne des espérances pour un traitement plus efficace de la syphilis primaire prise au début.

3) L'expérience obtenue à date dans le traitement de 227 cas d'intoxication arsénicale par le BAL semble suggérer qu'il a une certaine valeur dans de tels cas. La mortalité est réduite de beaucoup et la guérison est habituellement accélérée. Une méthode de traitement est décrite dans le texte.

R. Brault, M.D.

## Resumen

El presente artículo es un resumen de algunos estudios recientes sobre el uso de los arsenicales en el tratamiento de la Tripanosomiasis y de la Sifilis y sobre la detoxificación del arsénico por el BAL.

1) El acido p-arsenosofenilbutírico se ha encontrado efectivo en el tratamiento de la Tripanosomiasis reciente. Casos recientes pueden curarse en 1 o 2 semanas por medio de inyecciones diarias de 1 o 0.5 mg. por kg. de peso, respectivamente.

2) El Mapharsen y la penicilina son sinérgicos (se ayudan mutuamente) en el tratamiento de la sífilis experimental hasta el punto de que su uso en combinación es una vía prometedora para un tratamiento más efectivo de la sífilis reciente.

3) La experiencia hasta la fecha en 227 casos de intoxicación arsenical tratados con BAL (2,3 dimercaptopropanol) sugiere que su uso es útil en estos casos. La mortalidad se ha reducido significativamente y el restablecimiento se hace generalmente más rapido. Un programa de tratamiento se esboza en el texto original.

J. M. Taveras, M.D.

# The Cellular Mechanism of Recovery after Treatment with Penicillin

## I. Subacute Bacterial Endocarditis[1,2]

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THE efficacy of a therapeutic agent may be evaluated in a number of different ways. The usual method is to observe the effect on the clinical course of the disease and determine the per cent of patients who develop sequelae, and the mortality rate with and without the agent. In this paper, a little used but exceedingly valuable method of evaluation will be presented—the study of tissues from patients who have been treated with some therapeutic agent and subsequently die of the primary disease or of a complication.

This approach has the advantage of demonstrating the cellular mechanism by which a therapeutic agent facilitates healing. In this manner more may be learned of the nature of the disease, how progress of it is halted, and how repair is accomplished. Then the physician is in a position to employ the therapeutic agent more effectively or to reinforce the specific treatment with other agents.

### BASIS OF STUDY

My interest in the process of healing after treatment with penicillin which led to the following investigation was first aroused in January 1943. At that time the Department of Pathology at the Washington University School of Medicine performed an autopsy on a young woman, 33 years of age, who presumably had an induced abortion. On admission to the Barnes Hospital on December 26, she stated that she had had prolonged vaginal bleeding which started a few days before her expected menstrual flow on December 19. Twenty-four hours before admission she experienced a severe shaking chill and thereafter had a fever. To summarize briefly, the physical signs and the course in the hospital were those of a staphylococcal septicemia with endocarditis. Cultures of the blood, sputum, urine and uterine canal were positive for a hemolytic Staphylococcus aureus. She was given penicillin for five days for a total dose of 320,000 units. The blood culture became negative on the second day of treatment and remained so until death on January 2, seven days after entry and five days after penicillin was first given.

The immediate cause of death was cerebral hemorrhage, probably from rupture of a mycotic aneurysm or erosion of an artery by an abscess, although neither of these could be demonstrated.

The histologic structure of the cervix, endometrium, a small bit of retained placenta, ovary with a corpus luteum, breast, and pituitary indicated that the woman had been pregnant for approximately three months and that an interruption of the pregnancy occurred about ten to twelve days before death and was followed by an infection. The lesions of greatest interest were in the heart and the kidneys.

Three vegetations on the thickened mitral valve were not unusual in gross appearance. Microscopically they were not typical of acute bacterial endocarditis. The most conspicuous difference from the characteristic appearance was the absence of a layer of bacteria and fibrin on the surface. A culture showed a few staphylococci, and in sections stained for bacteria a few gram positive cocci were observed.

The kidneys were enlarged, and over the surface were numerous small—1 to 2 mm. in diameter—depressed, red foci. The foci were collections of lymphocytes, plasma cells and a few leukocytes with minimal necrosis.

Although there are other possible explanations

[1] This investigation has been carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Washington University.

[2] Delivered before the Section on General Medicine of the College of Physicians of Philadelphia, January 28, 1946.



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of these observations on the heart and kidneys, it seemed at that time that both might be considered as healing or abortive variants of staphylococcal pyemia.

## PLAN OF STUDY

Because of the interest this case aroused, thereafter the autopsies on patients treated with penicillin at the Barnes Hospital were studied a little more than was required by routine demands. It became apparent that a satisfactory study could not be made on the limited material of one hospital. Accordingly an application was made to the Committee on Medical Research of the Office of Scientific Research and Development. The suggested investigation contemplated collection of histories, autopsy protocols, and tissue from all hospitals in which penicillin was used in 1943 and 1944, this investigation to be conducted under the auspices of the Committee. The proposal was authorized, and in the fall of 1944 the materials for study were secured in visits to twelve hospitals and schools, the staffs of which were most cooperative.

Over one hundred cases were available for study in four categories: subacute bacterial endocarditis, pyemia, pneumonia, and meningitis, of which the first—subacute bacterial endocarditis—illustrates most of the general principles and will be discussed in this paper. No review of the literature is included but only personal observations, many of which have been made previously by others.

As a control, eight cases from the files of the Department were studied. These patients died between 1933 and 1935 and received no specific therapy.

## THE NATURE OF THE VEGETATION IN ENDOCARDITIS

As the study proceeded it became increasingly clear that the observations could not be explained if the usually accepted idea of the nature of a vegetative endocarditis were accepted. In most textbooks the terms vegetation and thrombus are used interchangeably, and it is stated or implied that the vegetation is a thrombus.

In a perfectly formed vegetation of bacterial endocarditis, acute or subacute, there are three definite layers: (1) a large central mass of necrotic, relatively acellular, fibrillated debris; (2) a more peripheral layer of bacterial colonies; and (3) a most peripheral layer of delicate fibrillary acellular material. There are slight differences in layers 1 and 3, but superficially they appear similar. If a vegetation is stained for elastic fibrils or for collagen, fragments of these are seen in layer 1 but not in layer 3. Further, stains for fibrin show a network in both, but in layer 1 the threads of fibrin constitute a small part of the total mass.

Since elastic and collagen fibrils are observed regularly in the central core of the vegetation, which constitutes three quarters to seven eighths of the total, it logically follows that this part is necrotic tissue and not thrombus. Careful study of the pattern of the fibrillary structure further confirms this. The whorls are identical with those present in the valve of chronic endocarditis.

Discussion of the implications of this conclusion on the pathogenesis and postulated growth of vegetations will be postponed until presentation of the observations on healing of subacute bacterial endocarditis.

## EFFECT OF TREATMENT WITH PENICILLIN ON SUBACUTE BACTERIAL ENDOCARDITIS

From the twenty-two cases studied, five have been selected which illustrate the essential features.

Case No. 1. Barnes Hospital Autopsy No. 11,617. A 56 year old white woman was admitted to the hospital on March 14, complaining of exertional dyspnea and pain in the cardiac region since childhood; weakness, loss of weight, and chills and fever for six months; and abdominal pain and swelling of the legs for two months.

There were petechiae in the conjunctivae and on the fingers and toes. The heart was slightly enlarged. The liver and spleen were palpable and tender. Blood cultures showed Actinomyces bovis and alpha hemolytic streptococci. Beginning on March 15, the patient was given 40,000 units of penicillin intramuscularly every two hours for four days without benefit. Sulfadiazine was then given and levels of 10 to 15 mg. per cent obtained. On March 23 penicillin was begun again at 40,000 units every two hours and increased to 80,000 units every two hours on March 26. Many embolic phenomena developed and cardiac failure increased. The patient died March 30. Penicillin was last given one hour before death, and the total dose was 6,720,000 units.

The anatomic diagnosis included: chronic endocarditis of the mitral and tricuspid valves; subacute bacterial endocarditis of the tricuspid and mitral valves and posterior wall of the left atrium;

infarcts of the heart, spleen, liver and kidneys; and focal embolic glomerulonephritis.

of closure, and a larger pedunculated vegetation nearer the base. Figure 2 (designated as area

PLATE I

FIG. 1. (Upper right) (Case 1.) Two vegetations of subacute bacterial endocarditis on the mitral valve; one pedunculated, and one sessile.

FIG. 2. (Upper left) (Case 1.) The stalk of the pedunculated vegetation from region 2, marked on Fig. 1. Note the tissue in the superficial parts on both sides, and the central necrotic core.

FIG. 3. (Lower) (Case 1.) Higher power view of region 3, marked on Fig. 1. The tissue on the left is approaching the bacterial colonies on the right. Note that the bacteria have disappeared from the part of the vegetation already organized.

A section of the mitral valve (figure 1) shows two vegetations, one sessile mass near the line

2 in figure 1) shows the entire thickness of the pedunculated vegetation. There are thin layers

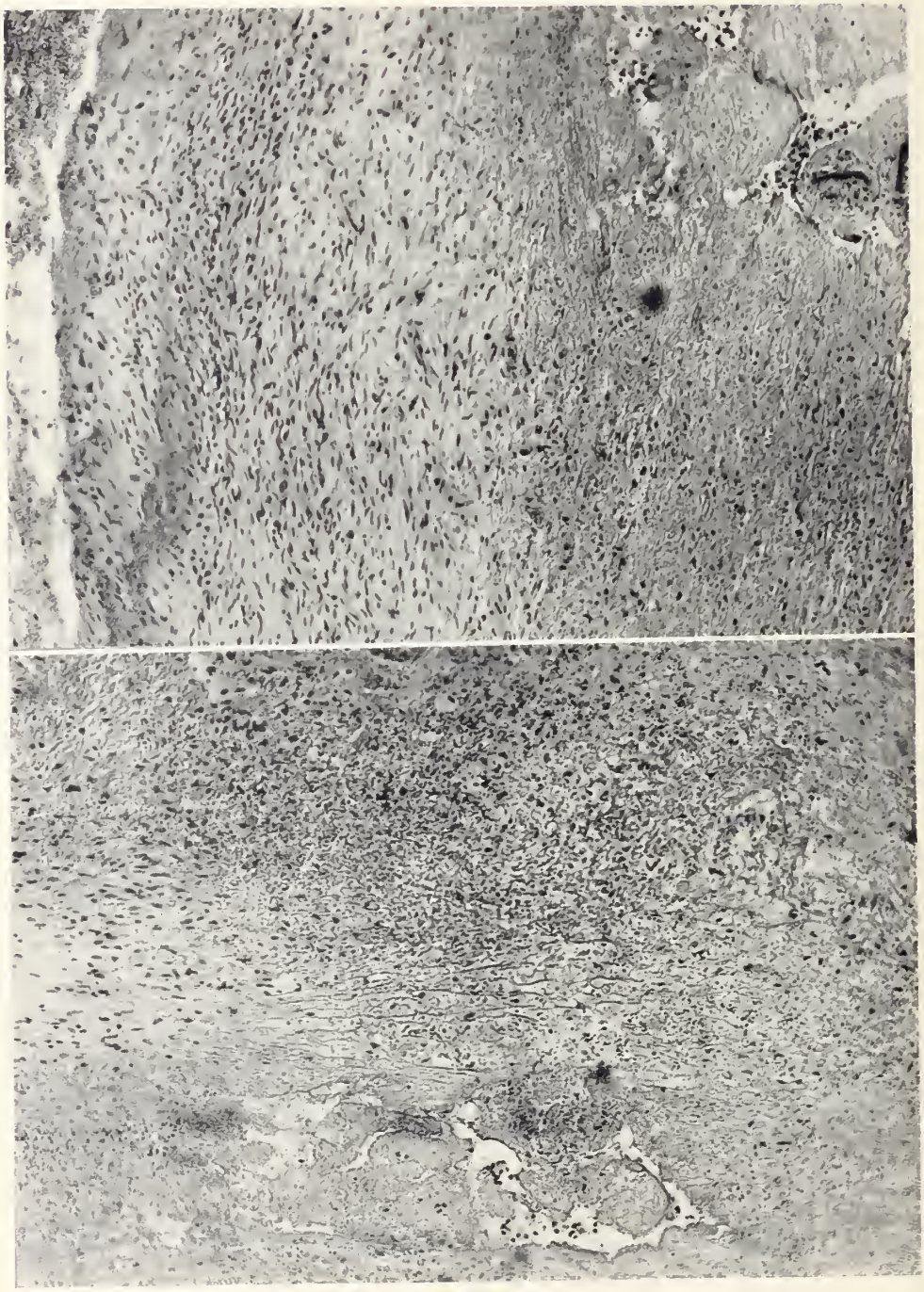

PLATE II

FIG. 4. (Upper) (Case 1.) Higher power photomicrograph of region 4 in Fig. 1. The superficial part of the vegetation is composed of a loose fibroblastic tissue with a distinct line of demarcation from the underlying necrotic core.

FIG. 5. (Lower) (Case 1.) Appearance of the more distal extention of the tissue in Fig. 3. As in Fig. 4 there is a sharp demarcation between the tissue and the necrotic core below.

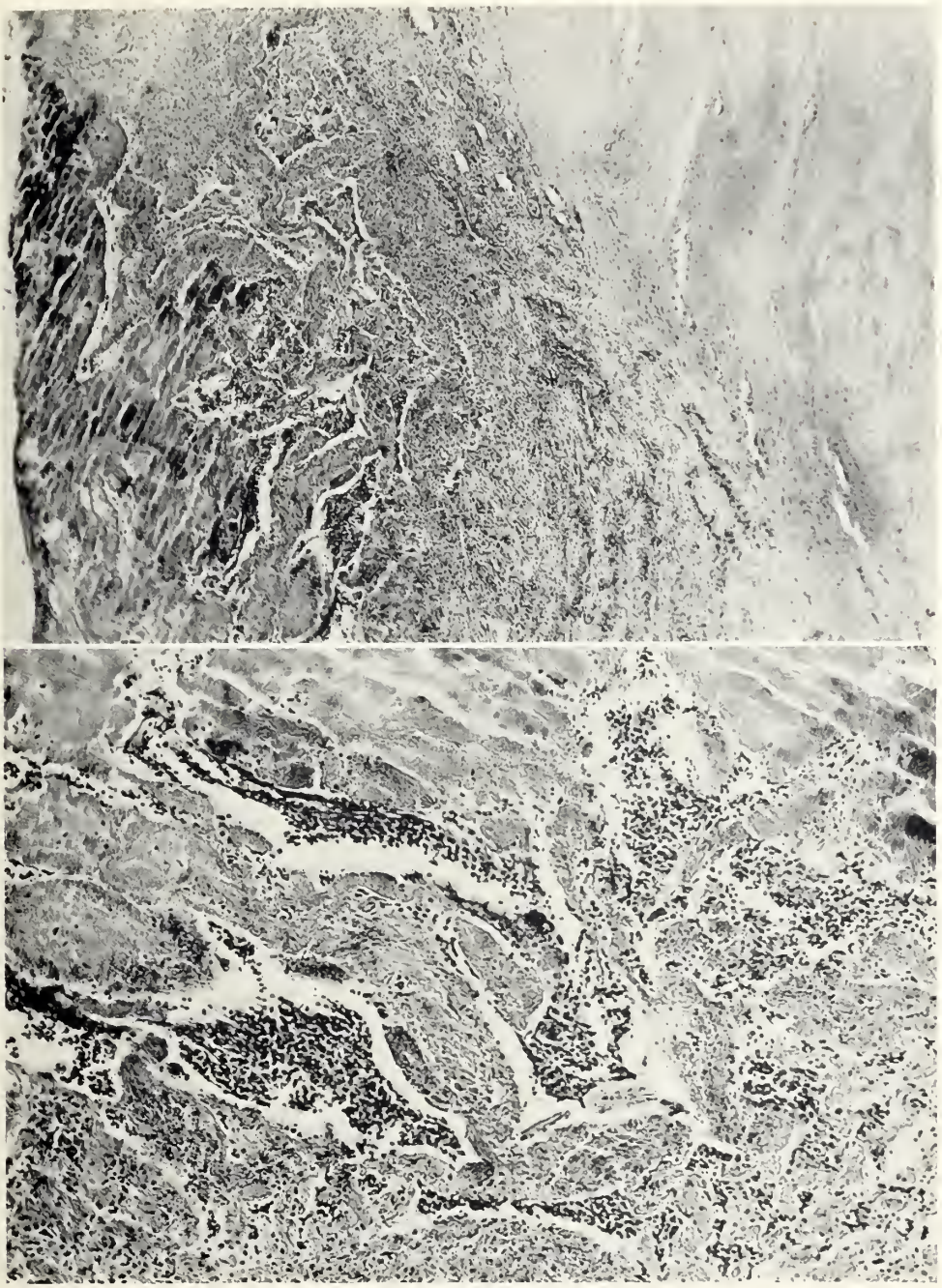

PLATE III

FIG. 6. (Upper) (Case 1.) Low power photomicrograph of the sessile vegetation designated as region 6 on Fig. 1. Superficially to the left there are fibrin and bacterial colonies. In the right there are many leukocytes and granulation tissue. On the extreme right is the fibrotic valve.

FIG. 7. (Lower) (Case 1.) A higher power photomicrograph of the central region of Fig. 6. Note the clefts filled with polymorphonuclear leukocytes representing destroyed bacterial colonies.

of tissue on each side enclosing a necrotic centrum. The granulation tissue extends outward on the surface to a point just short of the large bacterial masses (figure 3, designated as area 3 in figure 1). A higher-power view of the superficial tissue and deeper necrosis of area 2 is given in figure 4. The junction of the tissue with the necrotic bulbous end of the vegetation is depicted in figure 5.

The appearance of figures 1 to 5 may be explained as a proliferation of tissue through the superficial layer of fibrin and bacteria. As the capillary vessels, fibroblasts, and leukocytes advance, the bacterial colonies are destroyed. In this vegetation the process has extended about two thirds of the way from the base to the apex of the vegetation.

In some instances organization may also proceed from the entire base of the vegetation. In the sessile vegetation there are successive layers of dense connective tissue, granulation tissue, lacunae filled with leukocytes, and bacterial colonies embedded in a granular debris (figure 6, designated 6 in figure 1). The lacunae (figure 7) probably represent former bacterial colonies which have been phagocytized and destroyed.

Case 2. Barnes Hospital Autopsy No. 11,779. A 55 year old white man was admitted to the hospital on May 8, 1945. Five years previously he had a left-sided hemiplegia, with almost complete recovery except for general weakness until six weeks previously when he began to notice swelling of the feet and ankles and an increasing number of petechiae. More recently he had difficulty in speaking clearly.

On May 14 a blood culture showed alpha hemolytic streptococcus. Penicillin was started May 17, 40,000 units every two hours intramuscularly for fourteen days. The blood cultures remained positive. On June 1 penicillin was increased to 50,000 units every hour. The organism was then found to grow in concentrations of 20 units of penicillin per cubic centimeter. Penicillin was stopped on June 5 and begun again, 50,000 units every hour, on June 12. On June 17 test injections of 100,000 units were given intravenously every two hours and blood levels taken. Five minutes after injection the level was about 16 units per cubic centimeter. On June 18, 50,000 units every hour intramuscularly were begun again and continued until June 20, for a total of 22,610,000 units.

At that time the patient refused further injections of penicillin and signed himself out of the hospital, under protest, June 28. He was readmitted July 22, the edema worse, the petechiae more abundant, small pustules on both hands, and complaining of shortness of breath. No chemotherapy was attempted because of evidence of extreme renal and hepatic damage. The patient developed pulmonary edema on July 31 and died on August 1.

The anatomic diagnosis included: chronic endocarditis of the mitral valve; subacute bacterial endocarditis of the mitral and aortic valves and wall of the left auricle; subacute bacterial endarteritis of the aorta; recent and healed infarcts of the spleen and kidneys; focal encephalomalacia of the occipital lobes and left cerebellum; focal embolic glomerulonephritis; and miliary abscesses of the myocardium.

Sections from the vegetation on the mitral valve show well the process of phagocytosis of bacteria, destruction of the colonies, and formation of lacunae. In figure 8 part of the colony has been destroyed and the remainder broken into smaller fragments. A large lacuna with only a small mass of bacteria at one side is depicted in figure 9. As the colonies are destroyed, large numbers of bacteria are seen in phagocytes (figure 10). The same phenomenon is present in the mural vegetations of the left auricle in this heart (figure 11).

The observations illustrated in figures 6 and 7 from case 1, and figures 8 to 11 from case 2 may be explained as phagocytosis of the bacterial colonies when living tissue reaches the proximity of the bacteria. The end result is a lacuna surrounded by necrotic vegetation or tissue.

Case 3. Barnes Hospital Autopsy No. 11,103. A 68 year old white woman was admitted to the hospital January 27, complaining of fever and malaise of two and a half months' duration. The blood culture showed Streptococcus viridans. February 8 the patient was transferred to another hospital and after three weeks with no improvement, returned home. On March 15 the patient was readmitted to Barnes Hospital for penicillin therapy. She was disoriented and unable to speak or turn her body. There were many petechiae on the conjunctivae, face, trunk and extremities, and the feet were swollen. The blood culture showed Streptococcus viridans. Penicillin was begun on March 17, 25,000 units every two hours intramuscularly. On March 20 the blood culture was negative, but the patient failed to improve and died on March 23. Penicillin was last given five

hours before death, and the total dose was 1,700,000 units.

endocarditis of the mitral valve; partially healed infarcts of the spleen and kidneys; focal embolic

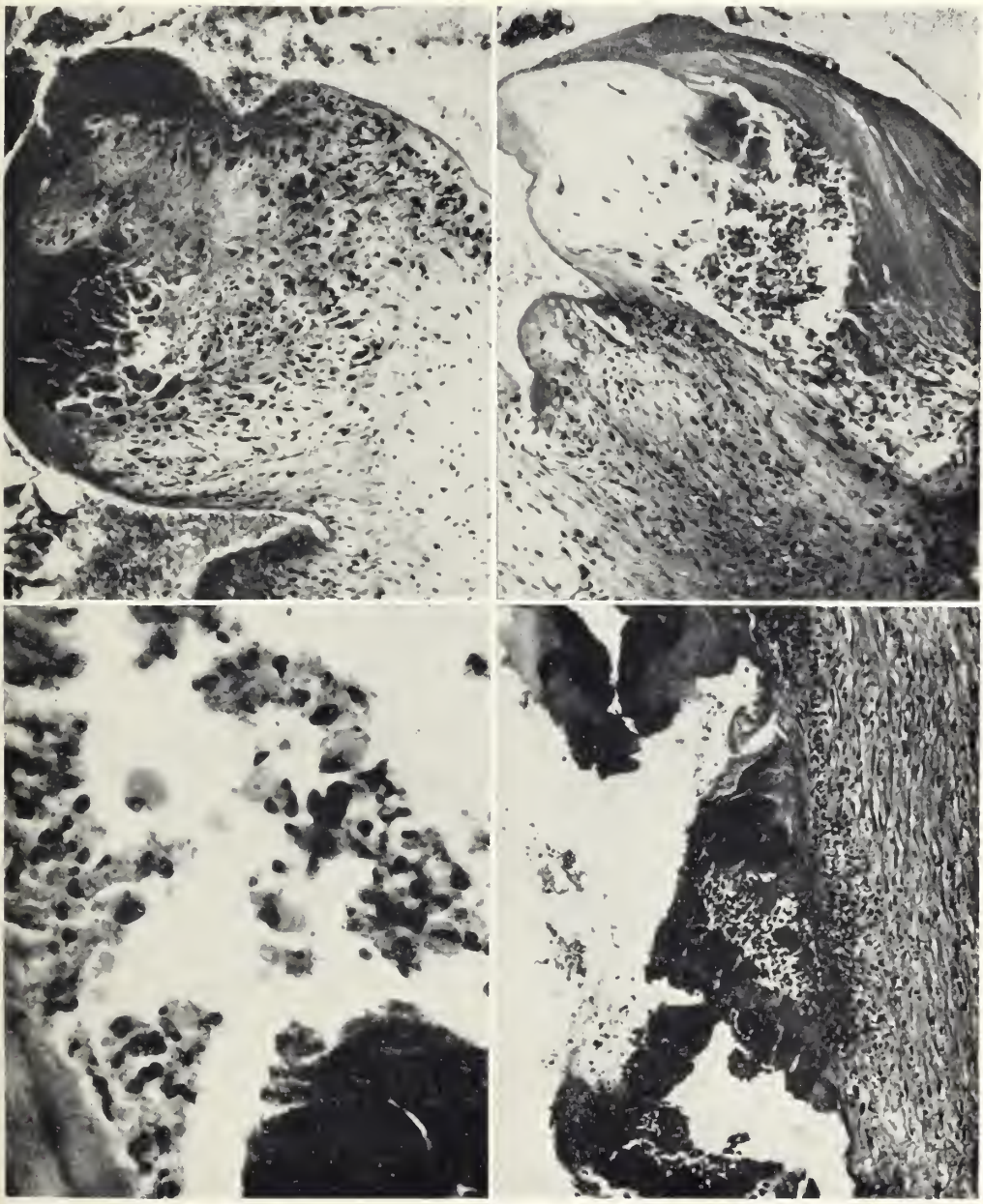

PLATE IV

FIG. 8. (Upper left) (Case 2.) Partial organization of a bacterial colony.

FIG. 9. (Upper right) (Case 2.) Clear area in the superficial part of the vegetation partially filled with leukocytes and with the remnants of a bacterial colony.

FIG. 10. (Lower left) (Case 2.) Active phagocytosis of bacteria about a large colony.

FIG. 11. (Lower right) (Case 2.) Invasion of the bacterial colonies from below in a mural vegetation on the wall of the left auricle.

The anatomic diagnosis included: chronic endocarditis of the mitral valve; subacute bacterial glomerulonephritis; and subarachnoidal hemorrhage.

There is a large partially organized vegetation on the mitral valve (figure 12). In the area outlined there is a sharp line of demarcation between the necrotic part and the proliferating fibroblasts (figure 13). This is taken to mean that the necrotic component of the vegetation organizes slowly or not at all. This conclusion is supported by the better known examples from general pathology of slow organization of the necrotic centra of caseous tubercles and gummas.

Case 4. University of Minnesota Autopsy No. 44-999. A 37 year old white woman was admitted to the hospital on May 5 with a three months' history of chills, fever, and weakness of the left side of her face, the right arm and right leg. Despite previous treatment with large amounts of sulfanilamide in another hospital, the blood culture showed Streptococcus viridans.

The heart was enlarged to the left, the liver and spleen were palpable, and there was a large umbilical hernia. There were many petechiae on both conjunctivae. Penicillin was started May 6 and given intravenously, 100,000 units every twelve hours. The patient improved and the blood culture showed no streptococci after twenty-four hours. New petechiae appeared in the conjunctivae, however, and on May 30 the patient suddenly developed sharp abdominal pain localized in the umbilical region. An exploratory operation, performed because of the possibility of a strangulated abdominal hernia, revealed a generalized peritonitis. The patient expired on the table. Penicillin had been continued to the day of death, the total dose being 4,200,000 units.

The anatomic diagnosis included: chronic endocarditis with involvement of the mitral valves; subacute bacterial endocarditis of the mitral valve; suppurated infarcts of the spleen with rupture and peritonitis; embolic glomerulonephritis; bilateral pulmonary atelectasis; and acute arteritis of the hepatic artery with thrombosis.

This case is used to illustrate advanced healing of a small vegetation. In figure 14 there are three distinct strata: a central calcified core, a middle layer of hyalinized and necrotic tissue, and a superficial layer of loose proliferating fibrous tissue.

The appearance in figure 14 could be compared to that in figure 2, if the central part of the latter were to become compacted and the centrum to calcify.

Figure 15 is from a case not given in detail (University of Minnesota 44-1468) to show calcification of an individual bacterial colony.

Case 5. Barnes Hospital Autopsy No. 11,358. A 46 year old white man was admitted to the hospital July 3, complaining of pain and edema in the left leg for one month, exertional dyspnea for three weeks, and a pruritic rash for three days. The patient had an attack of rheumatic fever at 21 years of age and another a year later.

The heart was enlarged and there was a harsh systolic murmur over the precordium. The liver was enlarged. On July 5 a blood culture showed hemolytic streptococci, the patient had a fever, and the spleen was palpable.

On July 15 penicillin was started, 20,000 units every two hours intramuscularly. After July 16, the next day, all blood cultures were negative and the temperature was normal. Penicillin was discontinued August 9, after a total of 6,080,000 units had been given in twenty-six days. The patient was discharged, improved, on August 23.

He was readmitted August 30, complaining of increased dyspnea and edema of the ankles. On September 20 the patient had a sudden attack of pulmonary edema and died shortly afterwards.

The anatomic diagnosis included chronic endocarditis of the aortic valve with calcification and partial obliteration of one commissure.

The aortic valve (figure 16) is greatly deformed with a thin base and a large bulbous calcified edge. The calcified masses are surrounded by a loose fibroblastic tissue infiltrated with lymphocytes and large mononuclear cells (figure 17). In other regions, especially near the surface, there are endothelial-lined spaces (figure 18), variable in size and outline but corresponding in general architectural pattern to the lacunae left by destruction of bacteria shown in figure 7. The surface is lined by endothelium, and all evidence of a vegetation is absent.

The observations of this valve with advanced healing serve to confirm the conclusions reached from study of the earlier stages of healing seen in the other cases. The vegetation organizes or calcifies, and the bacteria are destroyed and the spaces occupied by them become endothelized.

## HEALING IN SUBACUTE BACTERIAL ENDOCARDITIS

On the basis of these observations, healing in subacute bacterial endocarditis may be arranged as five processes: covering of the exposed surface of the vegetation with fibrous tissue, invasion of

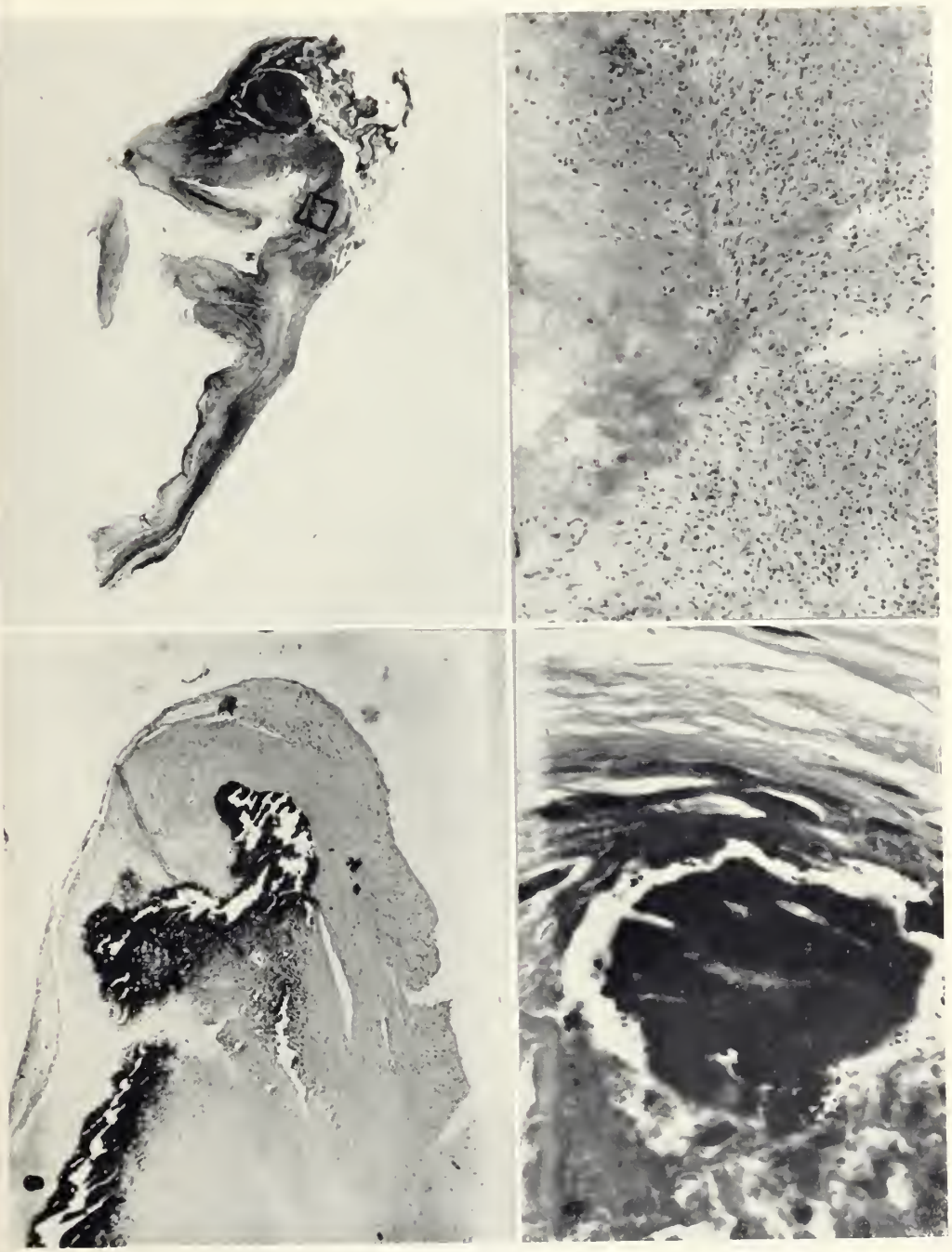

PLATE V

FIG. 12. (Upper left) (Case 3.) Partially organized vegetation on the mitral valve.

FIG. 13. (Upper right) (Case 3.) From the designated region on Fig. 12 to show the sharp line of demarcation between the necrotic part of the vegetation and the organizing part.

FIG. 14. (Lower left) (Case 4.) Calcification of the central part of a completely organized vegetation surrounded by a layer of collagenous connective tissue, and covered on the surface by a loose fibroblastic tissue.

FIG. 15. (Lower right) (Case not given in detail.) Calcification of a bacterial colony.

the layer of colonies and phagocytosis of bacteria, calcification of bacterial colonies, hyalination and calcification of the central core of the vegetation, and endothelization of the spaces and clefts in the vegetation.

In order to understand the first—covering of the exposed surface of the vegetation with fibrous tissue—it is necessary to return to the discussion of the nature of the vegetation in bacterial endocarditis. To recapitulate, it is composed of a central core of necrotic tissue, a layer of bacterial colonies embedded in fibrin, and a superficial thin layer of fibrin. The necrotic core is similar to other foci of dead tissue such as the caseous nodule of tuberculosis. There is no network of fibrin on which an invading granulation tissue may form. Hence it undergoes organization slowly or not at all. On the other hand the superficial layer is fibrin and is readily and quickly replaced by fibrous tissue. The determining factor is the state of the fibrous tissue at the edge of the vegetation. If this region is well vascularized and if the fibrous tissue is not too collagenous and hyalinized, proliferation will proceed from some or all directions. In time the central core will be completely covered. Concurrently the fibrous tissue about the base of the vegetation is active in isolating the necrotic mass and invading it along the few septa and at places where a network of fibrin exists. The end result is a central necrotic mass completely surrounded by tissue.

The second process—invasion of the layer of colonies and phagocytosis of the bacteria—is a phenomenon seen in all bacterial diseases. In the absence of a specific chemical or biologic agent which will kill bacteria, the only method for disposal of the bacteria is to bring active phagocytes to the infected focus. In subacute bacterial endocarditis of a valve, this is not possible until the first process—covering of the surface with tissue—has taken place. A possible alternate is organization of the necrotic center, but it has been pointed out that this does not occur except in small superficial vegetations. In other words, leukocytes cannot migrate through the necrotic core, nor will they go through the superficial layer of fibrin from the blood in the cavities of the heart in sufficient numbers. That the latter is attempted is suggested by the alinement of leukocytes on the surface of the vegetation. As fibroblasts and capillaries replace the peripheral layer of fibrin, the adjacent bacterial colonies are broken apart and the bacteria are phagocytized and destroyed, at least in large part.

For reasons not apparent from the histologic study, some bacterial colonies undergo calcification—the third process. Perhaps the bacteria die and attract calcium salts in the same manner that necrotic tissue does.

The fourth process—hyalination and calcification of the necrotic part of the vegetation—is an undesirable feature of healing. As previously pointed out, necrotic tissue is not ideal soil for organization. There is no preexistent framework of fibrin for the fibroblasts and capillaries. Therefore there is encapsulation with hyalination and calcification. This process does not involve any significant degree of contraction or decrease in size. Hence the end result is a greatly deformed nodular valve, similar to that of calcific stenosis.

As the bacterial colonies are destroyed and as the necrotic core becomes lobulated, clefts and spaces appear in the vegetation. Endothelial cells from the surface or from sprouting capillaries grow into and line the spaces—the fifth process.

In summary, healing in subacute bacterial endocarditis is essentially the conversion of a vegetative endocarditis into a chronic endocarditis characterized by superficial vascularized connective tissue and central nodular calcification. Only time will tell whether or not the latter disease is functionally significant. Reports so far suggest that some patients develop cardiac failure as a result of the calcific stenosis, as did one of the patients reported on in this paper.

### TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

Comparison of the observations in those patients treated with penicillin and in those patients who received no specific therapy indicates that there is some evidence of healing in all, regardless of the form of treatment. However, more advanced healing is observed after treatment with penicillin.

Logically there are four possible procedures by which healing might be facilitated: (1) Control the further growth of bacteria; (2) bring phagocytes to the bacteria; (3) promote the growth of granulation tissue; and (4) aid in the final disposal of necrotic tissue.

Clearly, penicillin is effective in the first—control of further growth of bacteria. This inhibition, regardless of how produced, will be reflected in greater phagocytosis and proliferation of tissue since both are unfavorably influenced by active

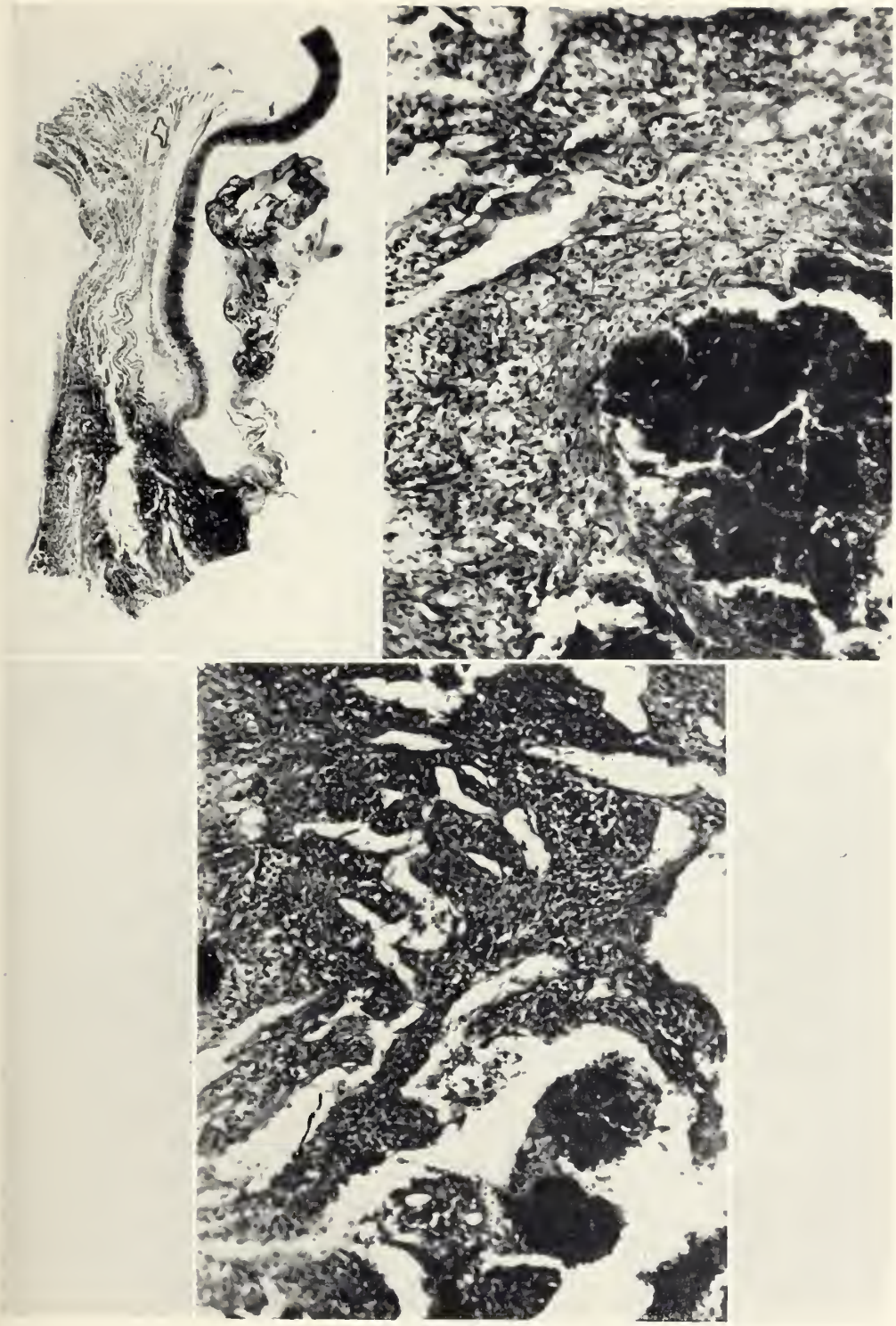

PLATE VI

FIG. 16. (Upper left) (Case 5.) Calcified nodules of the aortic valve in a patient who died two months after apparent cure of subacute bacterial endocarditis.

FIG. 17. (Upper right) (Case 5.) A calcified nodule surrounded by loose connective tissue.

FIG. 18. (Lower) (Case 5.) Large endothelial lined spaces in the superficial part of the aortic valve shown in Figure 16.

multiplication of bacteria. The sooner the inflammation is brought to a standstill, the more effective the final disposal of the necrotic debris. Hence, penicillin by an action of simple bacteriostasis exerts an effect on all aspects of healing. Therefore, in the sections from patients treated with penicillin there is more extensive and advanced healing than in those not so treated.

The dose and duration of treatment are largely outside the domain of the pathologic anatomist. However it is suggested that a blood level effective bacteriostatically on the organism of the patient be maintained for the period it takes for the layers of bacterial colonies and fibrin to be replaced by tissue. The actual range is probably 200,000 to 1,000,000 units per day in not less than six divided doses intramuscularly for three to six months.

This study was originally undertaken to determine whether or not better forms of treatment could be developed. Penicillin has a direct effect on only one of the four possible modes of attack. Perhaps when really effective agents become known, it may be possible to accelerate the phagocytosis.

Some of the factors determining the healing of wounds are already understood. The vegetation is a wound which must be healed in part by fibrosis. Among other things, an adequate supply of protein and vitamin C is necessary for rapid proliferation of normal fibroblasts. The most careful attention should be given to the nutritional status of the patient with subacute bacterial endocarditis, particularly to the level of the plasma albumin and to the adequacy of available vitamin C.

If the vegetation is largely necrotic tissue, it follows that it does not grow by addition of fibrin on the surface. Hence there is no basis for the use of an anticoagulant such as heparin to prevent a process which does not occur.

Whether or not it is feasible or desirable to accelerate calcification, will be left for others to decide. It has been reported that calcification of caseous tuberculous nodules in rabbits may be hastened by a high calcium diet and vitamin D. Perhaps a similar procedure initiated toward the end of active treatment would be worthwhile. Possibly further research may reveal a technique for disposal of the necrotic tissue which does not lead to calcification and deformation of the valve.

## PATHOGENESIS OF SUBACUTE BACTERIAL ENDOCARDITIS

It is not possible to study the "what"—that is, the pathologic anatomy of a disease—for long and not wonder about the how and why.

How and why do people develop subacute bacterial endocarditis? Of the thousands who have rheumatic fever, only a small percentage have this complication. Of the thousands who have a tooth extracted or have an acute upper respiratory infection, only a very few develop an endocarditis. Even when these two states, lesions of rheumatic fever and streptococci, are present together, the known incidence cannot account for the onset of subacute bacterial endocarditis.

The basic part of all vegetations is the same, the necrotic core of a valve. This is true for the verrucae of rheumatic fever, the so-called vegetation of nonbacterial thrombotic endocarditis, and for the lesions of bacterial endocarditis. Bacterial endocarditis differs from the others only in that there is a superficial layer of bacteria and fibrin. May it not be postulated, then, that bacterial endocarditis consists of two parts, a nonbacterial primary part and a bacterial secondary part?

It is well known that nonbacterial thrombotic endocarditis is a not uncommon observation at autopsy, in those who have died of debilitating diseases. Perhaps it occurs and heals more frequently than is suspected. It might account for the fibrous thickening of valves and adhesions at the commissures of the aortic valves observed in 60 to 90 per cent of all hearts at autopsy.

It is therefore submitted as a working hypothesis that if a person has a nonbacterial endocarditis, either rheumatic or thrombotic, at a time when he also develops a bacteremia with Streptococcus viridans, he or she may develop subacute bacterial endocarditis.

This would explain (1) the known association of lesions of rheumatic fever and subacute bacterial endocarditis in the same heart, (2) the frequency of lesions of subacute bacterial endocarditis on previously damaged valves, and (3) the low over-all incidence of subacute bacterial endocarditis in relation to previously postulated causal factors.

## SUMMARY

A comparison has been made of the lesions of the heart in subacute bacterial endocarditis in twenty-

two patients treated with penicillin and eight patients given no specific therapy.

Penicillin promotes healing in subacute bacterial endocarditis, but the basic processes of healing are not modified. These processes are: covering of the exposed surface of the vegetation with fibrous tissue, invasion of the layer of colonies and phagocytosis of bacteria, calcification of bacterial colonies, hyalination and calcification of the central core of the vegetation, and endothelization of the spaces and clefts in the vegetation.

In some patients, healing is accompanied by excessive calcification, and the result is a calcific stenosis of the valve.

It is postulated that the vegetative lesions of subacute bacterial endocarditis consist of two parts: a nonbacterial (rheumatic or thrombotic) primary part, and a bacterial secondary part.

# Atomic Energy and Cancer*

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I AM very pleased to have an opportunity to discuss with you this evening the concomitant developments in medicine and biology which occurred in exploring the field of atomic energy and which aided in the culmination of its primary objective, the Atomic Bomb. Since the activities of the Manhattan Project have become known, those of us in medicine, and particularly those of us interested in Cancer, have become alerted to the possibilities of usefully applying the information gained in the course of development of the Manhattan Project to various fundamental biological problems.

Emphasis to the present has been almost entirely on the destructive uses of atomic energy—and properly so—since the objective of the Manhattan Project was to develop a weapon which might contribute to an early close of the war. The results have etched their place in history. However, this tremendous release of energy which has been made possible by the attack on the nucleus, will not be reserved for destructive ends. There is another side of the story of atomic energy, a portion of which I would like to discuss tonight.

Although it appears that immediate uses for power, heat, etc., are still distant, the harnessing of atomic energy for useful purposes is now within our grasp. The unleashing of nuclear energy is certain to have broadened our horizon and made it brighter.

Before we survey the technics, the information and the material uncovered during the course of the Atom Bomb Project which might be applicable to the problem of cancer, I would like to show you an unusal film of the atomic bomb effects, heralds of the terror and chaos that will surely occur in future conflict. The full impact of the destruction of the atomic bomb has probably not yet been felt—politically, socially, economically. When it is, we will conclude that we must eliminate the use of atomic energy for destructive purposes. This now seems possible only by eliminating war itself. (At this point official Government films of the effects of the atomic bombings were shown.)

Broadly speaking, one might accept as a satisfactory solution to the cancer problem, either positive means of preventing the development of malignant tumors and associated diseases, or efficacious therapy which directly corrects the basic disorder. In order to do this, we must learn more of the nature of the development of neoplasms—their etiology, their biochemistry, the factors governing their growth; in other words, their fundamental metabolism. Although I hope to point out certain primary lines of approach, I feel that it would be presumptuous for me, in this uncharted field, to indicate how atomic energy will influence future cancer research and at what points the attack should be pressed. Instead, I prefer to tell you something of the character of the medical and biological developments which occurred in producing the atomic bomb and hope that this as yet uncatalogued mass of information may stimulate us in our untiring quest.

Early in the development of the Manhattan Project, it was recognized that many problems would arise which had not been previously encountered. These were concerned chiefly with: (a) The production and handling of radioactive material on a stupendous scale; and (b) the processing of uranium compounds, and the fabrication of uranium metal. As had been known earlier, uranium is a highly injurious nephrotoxic agent when introduced into the body.

On organizing the Medical Section, the extensive industrial installations and the large clinical facilities made it necessary to develop two large divisions to implement these activities—an industrial medicine unit and a clinical unit. A third division, a research unit, had already been established in order to investigate the medical and biological aspects of the various problems, anticipate the hazards to health, and institute the necessary safeguards. Of primary interest to the group here, are those developments which were made in the field of medical and biological research.

* Delivered at a joint meeting of the College of Physicians of Philadelphia and the Philadelphia County Medical Society, March 13, 1946.

In the research program, two primary problems as indicated before existed:

1. The problem involving the chemical toxicity of uranium and a great many other related compounds. Briefly, this required the establishment of tolerances for respiratory, gastro-intestinal, and skin absorption, a study of the methods whereby these materials could gain an entrance into the body, the development of the protective devices, and procedures for regular assay of these various materials. The mechanism of uranium toxicity was also studied.

2. The research on the radiation aspects is perhaps more directly applicable to Cancer research and therefore deserves elaboration. In general, the investigations were pursued along the following categories:

a. *Estimation of the Safe Levels of Radiation:* Because of the tremendous amount of radioactive materials which were encountered in the various operations, it was necessary to establish the accepted tolerances for radiation more securely. Investigations were therefore instituted for the study of gamma rays, neutrons, beta rays and alpha particles. Specific tolerance levels for radiation other than photons (x-rays and gamma rays) and neutrons were not established or had been only cursorily considered. The daily permissible radiation levels for alpha particles and beta rays are especially difficult to fix. Since alpha particles and beta rays are primarily of significance if introduced into the body, the kind of radioactive element, the rate of decay, the energy of the particle and localization of these elements in the tissues are important. (Skin effects due to external beta rays may constitute an important hazard.)

As you may know, the established tolerance for gamma rays and x-rays is .1 roentgen per day. The daily permissible dose of neutrons is .01 r (neutrons). Our data, obtained by investigating many species of animals, indicate that these levels are safe, and that definite safety factors are incorporated within them. In order to establish a tolerance level, or better, a daily permissible dose, it is necessary to determine all the possible effects of radiation. This includes general data on survival, specific effect on the hematopoietic tissue, specific effect on the reproductive system (the hematopoietic system and the gonodal tissues appear most sensitive to radiation) and the date of development of tumors, lymphomas, and blood dyscrasias during the lifetime of the animal. It has been possible to show that, in large amounts, external radiation and internal radiation due to the deposition of various radioactive materials can produce tumors. In the case of radioactive materials, these tumors develop at the points where the radioactive materials localize.

b. *Study of the Mechanism of Radiation Effects:* The empirical establishment of tolerance levels for radiation by studying survival, etc., is certainly a simple and direct approach. Nevertheless, profound knowledge of radiation injury will not be possible unless further studies into the mechanism of the biological effect of radiation are made. At present, the progress into the mechanism of radiation effect has not been extensive, but certain fundamental data have been accumulated in regard to the behavior of the various basic enzyme systems. There have also been studies on liver metabolism, kidney functions, blood cell metabolism, etc.

c. *Metabolism of Radioactive Materials:* In order to understand and anticipate some of the effects of radioactive elements introduced into the body, something of the metabolism of the fission products (about 30 elements in the middle of the periodic table which are produced in the production of atomic energy) needed clarification. It was also necessary to investigate in a similar manner certain alpha particle emitters which included plutonium and radium. It was necessary to know their mode of entry, the character of their radiation, the tissues in which they localize, the manner in which they are deposited in these tissues, and their excretion from the body. Under the auspices of Colonel Stafford L. Warren, Chief of the Medical Section of the Manhattan District, and particularly under the direction of Dr. Robert S. Stone, who was primarily concerned with the plutonium project, a great deal of information on the fission products, plutonium, radium, and uranium, has been collected. These data should serve as a fine background for further development in the study of radioactive materials in the body.

d. *Therapeutic Measures:* At the present time, we know of no specific therapeutic measure for combatting excessive radiation. Therefore, the greatest emphasis was placed on preventing personnel from encountering damaging amounts. In general, the approach has proven extremely effective. Nevertheless, some knowledge of the efficacy of various forms of therapy for radiation

injury would be a desirable adjunct to our other information. The primary attack has been along the lines of understanding the metabolism of sensitive tissue such as the hematopoietic structure.

e. *Assay of Radioactive Materials Deposited in the Body:* One of the very important studies in the research program of the Manhattan Project Medical Section, is the development of methods for the assay of excessive deposition in the body of radioactive materials of one type or another. As you well know, excessive amounts of radium deposited in the body can be estimated with a fair degree of accuracy by measuring radon, a gaseous daughter product of radium, present in the expired air. Similarly, by assay of the urine and other excreta for radioactive elements, the amount of these elements deposited in the body may be estimated. In order to do this, we need good excretion data, estimates of the tolerance levels and knowledge of the deposition in the body of these materials. I am pleased to say, that in a number of these problems, satisfactory solutions were developed.

I have here very briefly tried to indicate the general character of the medical research program of the Manhattan Project. We may now properly ask how this was related to the problem of cancer. What is the usefulness of materials used in atomic energy in the approach to cancer? Can the tremendous amounts of radiation be useful for cancer work? Why and how are the various devices which produce fissionable materials such as the uranium piles, the electromagnetic separation methods, and gaseous diffusion methods, useful for our purposes? The two general avenues which appear natural and promising for exploration and are most likely to answer our questions are, first, the application of radioactive elements to cancer therapy, and second, the study of the metabolism of malignant tumors by utilizing the radio elements and technics for searching and pertinent investigation.

Although radiation in the therapy of cancer is fairly well established and its use widespread, a variety of radioactive materials in large amounts, for external radiation and for internal therapy, can fortify the efficacy of radiation. This definitely promises to enhance our progress in the treatment of tumors. We have now an abundant and wide range of radiation energies and radioactive elements which may serve in the search for elements or compounds which might selectively localize in tumor tissue.

1. By introducing various materials into the pile and making use of the tremendous flux of neutrons, elements like cobalt and tantalum, which on activation have high energy photons, can be made available in large amounts for radiation purposes similar to that which the radium pack now serves. Materials like tantalum, can possibly be made into the form of needles and kept activated in the pile. They can then be used in the body for the same purposes served by interstitial radiation.

2. Specific radioactive materials such as $P^{32}$, $Sr^{89}$ $I^{131}$, can be produced in great abundance. During the past decade, $P^{32}$ has come into wide use in leukemias and polycythemias. $Sr^{89}$ had been used experimentally for bone tumors, because of its localization in the bone (its metabolism is quite similar to that of calcium). $I^{131}$ of course, localizing in the thyroid, may prove an important adjunct in thyroid malignancy. It has already been used successfully for hyperthyroidism.

3. Any of the various elements that can be made radioactive in the pile or are produced by fission in the pile, might conceivably be synthesized into compounds which would be localized in tumors. However, no one as yet has been able to produce an element or compound which is selectively localized in tumor tissue. If this were possible, radiation could be localized in tumors by this method. In addition, it might be possible to introduce elements into tumors which could be activated by neutrons and the resultant release of ionizing energy would be very destructive to the tumor tissue. For example, boron capturing a neutron will split up into several alpha particles, releasing a tremendous amount of intense ionization.

However, the exciting prospects in the abundance and variety of radio elements do not lie in the use of their radiation alone. They lie also in the fact that we are now in a position to make tagged elements in great quantity. These tagged atoms are isotopes of the ordinary elements, having the same chemical behavior. They can be recognized however, by certain additional and unique characteristics. There are two types of tagged elements—the stable and unstable isotopes. The unstable isotopes are radioactive and, therefore, can be identified by detecting their ionizing radia-

ion. The stable isotopes, having an increased mass, can be detected by devices, such as the mass spectrograph, which take advantage of the difference in masses. These tagged elements will undoubtedly revolutionize our ideas on fundamental metabolic problems, and specifically in the case of cancer, they offer a great hope in understanding its fundamental biology.

Radioactive isotopes can in general be utilized in the following broad ways:

a. By introducing radioactive materials into a living animal and subsequently examining isolated tissue for the quantitative deposition of the tagged element. An estimate of the uptake and distribution of these elements is then possible.

b. By utilizing radioactive elements which emit gamma rays. These can then be detected by proper instruments, without disturbing the body in any way. This permits body detection in the intact animal and may be applied readily.

c. By utilizing alpha and beta emitter deposited in tissue to affect photographic emulsion (radio-autographs). This method can be used to localize elements in tissues and possibly even cells, by making radio-autographs from thin sections of the tissue to be studied.

d. By tracing radio-elements to study character and rates of biochemical reactions, intermediate metabolism, exchange processes, secretion and excretion, reversibility, etc.

From the biological view point, the elements which are of interest group themselves in the following general order of importance:

a. Carbon
b. Nitrogen, Oxygen, Hydrogen
c. Sulphur (almost entirely in inorganic compounds)
d. Calcium, Phosphorus, Iron
e. Sodium, Potassium, Magnesium, Chlorine

Carbon easily heads the entire list.

Many of the radioactive elements, such as $C^{14}$ and $H^{3}$, together with $P^{32}$, Strontium$^{139}$ and Iodine$^{131}$, were known prior to the development of the Manhattan Project. However, due to the large scale on which uranium piles might be constructed, it would be possible to provide them in great abundance and provide them for many fields of research.

Radioactive isotopes, such as phosphorus, calcium, strontium, and iodine and the stable non-radioactive isotopes, such as carbon, hydrogen, oxygen, and nitrogen, have previously been used with great success in establishing complex and unknown behavior in certain metabolic processes. The element, carbon, is of particular interest to biologists, biochemists, biophysicists, and other scientists, because of its fundamental position in all our life processes. The basic and vital process of photosynthesis, upon which all life depends, may possibly be successfully attacked by tracing the element, carbon, throughout this cycle.

From the point of view of cancer research, the application of these isotopes to cancer investigations offers some hope of eradicating many of the hiatuses which exist in our knowledge of the vital processes of the tumor cell. The effect of various chemicals on tumor growth, the rôle of enzyme systems in tumor development, the part that specific elements in the diet may play in the Cancer Problem, and the activating impetus of certain carcinogenetic agents will now come under more careful scrutiny. This is to mention only a few directions of investigation. The carbon atom and the hydrogen atom, now recognizable in the midst of their complex activities, will immediately suggest many approaches. In the case of the Cancer cell, whose metabolism may differ from the normal cell in only a few, though fundamental, details, and where inquiries of the most searching and exacting nature are required, a highly critical tool for general use now appears.

## SUMMARY

I fear I have presented no startling or arresting information on the attack of the Cancer Problem. However, we have in general, brought to your attention two fields for development:

1. The first is the opportunity for improving the therapeutic approach. New radiations and new radioactive materials in an abundance which were not previously imagined, are now possible. These can be used for external radiation, for interstitial radiation and as radioactive materials in specific compounds which may be localized in various tissues.

2. A second and perhaps more important approach has been made possible by the ability to produce radioactive isotopes in abundance to study the unwarranted behavior of the cancer cell. The key to this probably lies in the use to which we may put $C^{14}$, but other elements (Hydrogen, Nitrogen, Sulphur, etc.) will be useful.

The success of the Manhattan Project in achieving its goal was unquestionably accomplished by difficult and intensive effort, but its success lies primarily in the fact that its development was based on certain fundamental and substantial corner stones. These were among others, the discoveries of fission and its attendant release of energy, the identification of fissionable materials, and the recognition of the possibility of a chain reaction. Although we have not yet uncovered similar fundamental corner stones in the approach to the cancer solution (perhaps from my limited vantage point, I do not recognize or appreciat them), real progress can be made by united an intensified efforts. We must impartially explor all fields; we must encourage, organize, an coordinate unhampered biological research; w must maintain that continuity which best assure full integration of all the data and informatio which may be developed. Once we gird ourselve to the task and pursue relentlessly all approache these fundamental corner stones will be uncovere and the solution we seek will not be denied us.

# Chronic Osteomyelitis as Depicted in a Suit for a Medical Fee in Massachusetts in 1660

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WHEN the patient is sick, the doctor is looked upon as a god; when the patient is improving and the fear of death is gone, the doctor is looked upon as an angel. When the patient is finally well, he looks upon his doctor as his fellow man; but when the doctor presents his bill, the patient looks upon him as a devil. This thought, so well expressed in literature and art of centuries long gone by, kindles a responsive chord in the heart of the physician today. The court records of our country are replete with cases in which the doctor is suing for his fee. In the early Massachusetts court records there is such a case which is of special interest for the light it sheds on the practice of medicine in New England in the seventeenth century.

The ailment in question was a chronic osteomyelitis in a child with a stubborn draining sinus and the extrusion of a large sphacelus nearly five inches long, after which fairly good healing apparently took place. An insight is afforded us as to the rôle of many women who acquired in those days considerable fame as healers of the sick. Of interest, too, is the fact that for better care the child was placed in the home of the doctress for treatment. In view of the precarious conditions of travel and the sparsely settled region in which the scene is set, it is easy to understand why the girl had to leave her home. A fee was demanded not only for the cure, but for board and lodging as well, just as it would be in our time. No doubt because of her poor state of nutrition she could not eat ordinary diet, as the witnesses declare, and the implication that special diet was considered important in the cure cannot be overlooked.

This case was diagnosed as "the King's Evil," which in later years came to be known as the scrofula. However, the King's Evil and scrofula pertained more especially to chronic draining tuberculous glands of the neck; when the Royal Touch became profitable, too much discrimination in diagnosis and treatment of the chronic wasting diseases in general was not evidenced. While John of Gaddesden in the *Rosa Anglica* of the 13th century, and subsequent writers, recommended that scrofulous patients go to the King to be touched, the first book on children's diseases to mention touching was that of Mercurialis in 1583. In 1664, about the period of this case under discussion, J. Starsmore wrote a book on children's diseases in English in which he described the King's Evil as a hard or schirrous tumor growing for the most part about the neck. Richard Wiseman, writing about the same time, voiced a general opinion when he stated that when the King's Evil mixes with marrow it always dissolves it and renders the bone carious. It was a long time before the usual form of chronic osteomyelitis was differentiated. The description and progress of the disease brought out by the testimony in this trial are unusually rich and lucid in detail, such as is rarely encountered in medical annals of our earliest colonial times.

Of course when the question of paying the bill came up, papa, who pays, took the girl to another doctor, Anthony Crosbie by name, for his opinion as to cure. (This is a common subterfuge in all cases of malpractice and was one of the important points of medical ethics corrected by the American Medical Association in the early days of its organization.) That worthy opined that the bone was not sufficiently "scaled," thus testifying that the conditions of the contract between doctress and patient were not fulfilled, for should the cure finally fail, then only the actual expenses of the child's board were to be incurred.

The treatment took eleven months and the expense (the price of a horse) was over twenty pounds, a right good sum of money in days when a laborer's hire might not amount to more than nine or ten pounds in a year. One doctor was said to have valued his services in such a case at fifty pounds, but we can lay this estimate to a layman's license. Twenty to thirty pounds was the usual salary for a year's service to a doctor at this period when he was regularly engaged to serve

the community on a contract basis. A horse was really a valuable piece of property in those days, when it was so hard to get around and help was very scarce. For the cure of his child it was alleged this father had proferred a colt valued at nine pounds. The colt grew up during the time of the treatment, so that afterward it was worth fourteen pounds. In other words, the longer the cure took, the greater the value attached thereto, for as the treatment proved more difficult and prolonged, the animal grew in vigor and value.

The first doctor to treat the child was Mr. Starr of Charlestown. This was Thomas Starr, who llived in Yarmouth from 1640 to 1670 and is called chirurgeon many times in the town records. He is called in the testimony a "noted practitioner." What treatments were utilized other than diets and dressings "which were oftentimes three persons, work," we are unable to tell. Some idea as to the variety of medicaments utilized in the treatment of the King's Evil and all "cankers, fistulas and old ulcers" can be partly deduced in the medical instructions which Edward Stafford sent Governor Winthrop.[1] Black powder made in the month of March by burning live toads with various concoctions could be both given internally and used "playster wise." In England the King was still touching the afflicted with miraculous effect.

There follows a transcript of the record of the case in vol. 2 of the *Records and Files of Quarterly Courts of Essex County, Massachusetts, 1656–1662*:*

1. (P. 195). "Ipswich, 1660.—William Edmonds V. Henry Greene for expenses about the cure of a child of his. Withdrawn. Plaintiff acknowledged several times that there was no bargain made with defendant." [William Edmonds also kept an Ordinary or Inn.]

2. (P. 226). "Ipswich 1660—Will Edmonds V. Henry Greene. For curing his daughter's leg, etc. Verdict for defendant.

"In the course of litigation for the fee, John Farnam said Green some years since had a daughter called Marie Green, sometime a patient under the hands of Mr. Starr, then of Charlesto. for the cure of a very dangerous sore leg, which daughter he brought to Ann Edmonds to be cured. For the cure, he proferred a certain mare colt valued at nine pounds, and afterwards at fourteen pounds, at which time Green also promised satisfaction for his daughter's diet, in case she should not be cured. It was also testified as to what some noted practitioners thought of said cure, that is Mr. Starr and Mr Crosbie, and for all which great care, trouble and costs in curing the said sore leg 'which all skilled in chirurgery know is more difficult then other parts of the body, in sundry respects', the said Green had withheld satisfaction. Plaintiff asked for payment according to the true worth of the said cure, Ann Edmonds affirming that it took eleven months and the expense was over twenty pounds.

"Matthew Price deposed that in 1657 he visited William Edmonds and saw Henry Green's daughter, Mary, who had formerly been under the care of Mr. Thomas Starre of Charlestowne, physician, for the cure of a sore leg. Deponent, upon looking at it, declared that it was in better condition than when under Mr. Starre's treatment, although it was a very bad and desperate wound. About a year after, deponent saw Mary Greene again and her leg was nearly well, and Goodwife Edmonds showed him a bone of five inches in length, which Mary said came out of her leg. There was very little soreness or pain in it, and she could leap about very lively.

"John Ilsly described the wound in the child's leg as a running sore.

"Giles Fifield deposed that Mary Greene was able to go up and down the house, wash dishes and sweep, when she was at his house in Charlestowne under treatment of Mr. Star.

"John Smith deposed that he was a boarder at the house of William Edmonds in Linn when Green's child was brought there and Goodwife Edmonds was to be paid for the cure and for diet.

"Joseph Edmonds testified as to the condition of the child when she came to his father's house and to the great care his mother gave her; that it was three person's work oftentimes to dress the wound and she could not eat ordinary diet. Anthony Crosbie, aged about 23 years, testified that he heard Goody Edmonds say that Henry Green's daughter's illness was the King's Evil and she had cured it. Afterward, said Greene brought the girl to Rowley and requested deponent to look at the leg, and according to deponent's best skill he thought that the bone was not sufficiently scaled.

"John Paul testified that Marie Greene showec him the bone which came out of the fore part o the leg and it was hollow at one end.

[1] Cf. Holmes, O. W., Proc. Mass. Hist. Soc., 1860–62.

* Published at Salem, Mass., 1911.

"Giles Fifield testified that the bone lay bare when Henry Green took his child to Charlestowne and a month after, as deponent was going to Lyn, he stopped at Edmond's house to see his cousin Mary Greene, Goody Edmonds said she hoped to have the child home in six weeks. The flesh was grown about one quarter inch upon the bone. When deponent returned to Charlestowne, he told Mr. Starr about the condition of the child's leg, and said Starr replied he would eat a firebrand if she cured it. Later, deponent's uncle told him that he was to give his mare's colt for the cure.

"Sarah Jenkins heard Dr. Crosby say he would not have done it for less than fifty pounds.

"Sarah Ormsbe deposed that Henry Green came into their house with his daughter, about the beginning of last April and showed the leg to Goodman Inslee. There was a plaster on it. Edmonds told Green that the child could be taken home for her leg was well, except that her shin was a little broken against a pot side."

# Transactions of the Sections

## SECTION ON GENERAL MEDICINE

*March 25, 1946*

HEPATITIS FOLLOWING BLOOD AND PLASMA TRANSFUSIONS. J Edward Berk, M.D. (Commentator: John R. Neefe*, M.D.) (*Abstract 1, below.*)

AN EVALUATION OF IMMUNE SERUM GLOBULIN AS A PROPHYLACTIC AGENT AGAINST HOMOLOGOUS SERUM HEPATITIS. Garfield G. Duncan, M.D. (Commentator: Joseph Stokes, Jr., M.D.) (*Abstract 2, below.*)

LEUKOPENIA: ITS CLASSIFICATION, ETIOLOGY AND TREATMENT. John S. Lawrence,* M.D. (Published in the *Transactions & Studies*, 4th ser., 14: 1–14, April, 1946.)

*April 22, 1946*

THE COMBINED INJECTION OF VITAMINS AND VACCINES, WITH A NOTE ON TYPHOID AGGLUTINATION TITRES. F. Maurice McPhedran, M.D. (Commentator: Samuel Bradbury, M.D.) (Published in this issue of the *Transactions & Studies.*)

THE HEART IN ACUTE POLIOMYELITIS. William I. Gefter*, M.D., William G. Leaman, Jr., M.D., Pascal F. Lucchesi, M.D., Irene E. Maher*, M.D., and Milton Dworin*, M.D. (Commentator: Thomas M. Durant, M.D.) (*Abstract 3, below.*)

PROTEIN METABOLISM IN THE COURSE OF LEUKEMIAS. Max M. Strumia, M.D. (Commentator: John Eiman, M.D.) (*Abstract 4, below.*)

PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA. Robert L. Mayock*, M.D., and Edward Rose, M.D. (Commentator: Stanley P. Reimann, M.D.) (*Abstract 5, below.*)

*May 27, 1946*[1]

CARCINOMA OF THE PROSTATE AND THE INHIBITION OF TUMORS. Charles Huggins*, M.D.

* By invitation.

## SECTION ON OPHTHALMOLOGY[2]

*March 21, 1946*

ANGIOID STREAKS OF THE RETINA ASSOCIATED WITH PERIPHERAL VASCULAR DISEASE. Harold G. Scheie, M.D., and Norman E. Freeman, M.D.

A COMPARISON OF THE OCULAR SIGNS IN CHILDREN AND ADULTS SUFFERING FROM SUBDURAL HEMATOMA. Frank B. Walsh*, M.D.

*April 18, 1946*

A CASE OF JOHNSON-STEVEN'S DISEASE: CASE PRESENTATION. Bruce A. Grove*, M.D., and Edmund Meisenhelder*, M.D. (Commentator John Wilson*, M.D.)

ACQUIRED OPHTHALMIC ALLERGY. William S. Bonner*, Major, A.U.S.

KERATITIS OCCURRING IN PATIENTS WITH LYMPHOGRANULOMA VENEREUM. Harold G. Scheie, M.D., and Alan S. Crandall*, M.D.

PIGMENTED NAEVUS OF THE IRIS TREATED BY IRIDECTOMY. James S. Shipman, M.D., and P. Robb McDonald, M.D.

## SECTION ON OTOLARYNGOLOGY[3]

*April 17, 1946*

CANCER OF THE PARANASAL SINUSES. John V. Blady, M.D.

CANCER OF THE ORAL CAVITY. Bernard P. Widmann, M.D.

(Commentators: S. G. Castigliano, M.D., J. W. Bransfield, M.D., G. M. Dorrance, M.D., and Karl M. Houser, M.D.)

[1] Joint meeting with the Philadelphia Urological Society.

[2] The transactions of this Section are customarily abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology.*

[3] The transactions of this section are customarily abstracted in the *Archives of Otolaryngology.*

## ABSTRACTS

*Abstract 1*

HEPATITIS FOLLOWING BLOOD AND PLASMA TRANSFUSIONS. J. Edward Berk, M.D.

Seventy two cases of hepatitis considered to follow blood and/or plasma transfusions have been observed. The data in 43 of the cases is analyzed. The group was made up of soldiers ranging in age from 19 to 37 years. Blood alone was received by

17.1 per cent and plasma alone by 26.8 per cent; blood and plasma were given to the remainder (56.1 per cent). The average amount of blood received was 1687 cc. and the average amount of plasma 756 cc. The interval between the first transfusion and the clinical appearance of jaundice averaged 103.9 days; the average interval between the last transfusion and the appearance of jaundice averaged 95.7 days. The jaundice averaged 35 days in duration with an average maximum serum bilirubin of 7.9 mg. per cent and an average maximum icterus index of 77. The liver was palpable in 60 per cent and the spleen in 22.5 per cent of the cases. Fever of 100 degrees F. or higher without other explanation was observed in 13.9 per cent. There was a tendency toward leukopenia and lymphocytosis. In some cases the lymphocytes resembled those seen in acute Infectious Lymphocytosis. Gamma globulin seemed without effect in reducing the incidence of the disease. There were four deaths representing a mortality rate of 5.6 per cent. The progress of the disease was rapid in the fatal cases averaging 7.7 days from onset of symptoms to death. The predominant lesion found at post-mortem examination was diffuse liver necrosis.

*Abstract 2*

AN EVALUATION OF IMMUNE SERUM GLOBULIN AS A PROPHYLACTIC AGENT AGAINST HOMOLOGOUS SERUM HEPATITIS. Garfield G. Duncan, M.D.

The potential danger of injecting an icterogenic virus with pooled blood or plasma makes it important to determine whether or not gamma globulin is an effective prophylactic agent against homologous serum hepatitis. Also, does the response to this agent add another difference between infectious epidemic hepatitis and homologous serum hepatitis?

Gamma globulin prophylactic therapy has been found effective against infectious epidemic hepatitis in four outbreaks (1, 2, 3, 4).

An increasing incidence of hepatitis, presumably of the homologous serum type, among battle incurred casualties prompted an evaluation of gamma globulin as a prophylactic and attenuating agent against this disease. This study was begun at England General Hospital on 3 April 1945.

The subjects were *battle casualty patients who had received blood or plasma* or both at the time of injury. It was among these patients that practically all the cases of hepatitis were appearing.

In order to detect early cases of the disease a specimen of urine was obtained from each patient of this group, and subjected to both the Methylene Blue Test and the Harrison Spot Test for bile pigment. Patients in whom these tests were negative were selected for the study. Patients who gave a history of having had jaundice, also, those who developed hepatitis within ten days after receiving the gamma globulin and those in whom more than five months had elapsed between the time the transfusion was given and the onset of hepatitis, were excluded from the series. Alternate patients were given a single dose of 10 cc. of gamma globulin, intramuscularly, while the alternating patients, not so treated, were used as controls.

The results up to and including 23 October 1945, are as follows:

(*Period 3 April–23 October*)

Treated Group (Total)

| | |
|---|---|
| No. of patients | 2,406 |
| Cases of Hepatitis | 29 |

Control Group (Total)

| | |
|---|---|
| No. of Patients | 2,374 |
| Cases of Hepatitis | 23 |

Of the total number of patients receiving gamma globulin (2,406), twenty-nine (29) or 1.2 per cent, developed hepatitis. Of the control group of 2,374 cases, twenty-three (23) or 0.9 per cent developed hepatitis.

In contrast to the previous findings of Grossman, Stewart and Stokes (5) concerning the use of gamma globulin at the McCloskey General Hospital in the prevention of homologous serum hepatitis, the incidence of hepatitis in the treated and untreated groups reported here was not significantly different. The only discernible difference between the method of study and the cases selected in the two hospitals was the injection of two doses, 10 cc. each, of gamma globulin at an interval of one month at the McCloskey General Hospital as opposed to a single dose of gamma globulin (10 cc.) at the England General Hospital. The lower incidence of hepatitis in the injected group, as compared to the control group, during the earlier part of our study at first suggested that the final results would be similar to those at the McCloskey General Hospital. That such was not the case, when the final results were tabulated,

indicated that a considerable lag had occurred in the onset of hepatitis in the injected group. This lag is demonstrated by the fact that the average number of days from the injection of globulin to the onset of hepatitis was 52 days, whereas, in the control group the onset of hepatitis averaged only 34 days from the time they were designated as controls. The significance of this difference is also confirmed by the fact that the average intervals between the time the two groups received blood or plasma as battle casualties and the time they were injected with globulin or designated as controls were almost identical.

### SUMMARY AND CONCLUSION

1. A single dose of 10 cc. of immune serum, gamma globulin, given intramuscularly to each of 2406 battle casualty patients who had received transfusions of blood or plasma, or both, within the previous six months, failed to reduce the incidence of hepatitis, presumably of the homologous serum type. Twenty-nine (29) or 1.2 per cent of these patients developed hepatitis in contrast to 23 or .9 per cent in 2374 similar patients used as controls.

2. The administration of the single dose of 10 cc. of globulin apparently retarded the onset of the acute phase of hepatitis by an average period of 18 days, a delay which is statistically significant.

3. The ineffectiveness of immune serum gamma globulin in a single intramuscular dose of 10 cc. for preventing homologous serum hepatitis presents another apparent difference between this disease and infectious (epidemic) hepatitis.

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*Abstract 3*

The Heart in Acute Poliomyelitis. William I. Gefter, M.D., William G. Leaman, Jr., M.D., Pascal F. Lucchesi, M.D., Irene E. Maher, M.D., and Milton Dworin, M.D.

The cardiac status of 467 patients with acute poliomyelitis is reviewed. This study was prompted by the high incidence of acute myocarditis in fatal cases of poliomyelitis (1, 2). Clinical abnormalities in 456 non-fatal cases were insufficient to warrant a diagnosis of myocarditis, which may exist, however, in the absence of clinical findings (3).

Abnormal electrocardiographic patterns were recorded in 32 (14.2%) of 226 patients. There was no correlation between the frequency of abnormal tracings and sex or age. The incidence of abnormal electrocardiograms rose significantly as the severity of the disease increased, and inconstantly as the febrile period lengthened. The effect of fever per se was eliminated as a possible factor. No significant change occurred in the frequency of abnormalities as the duration of illness increased, suggesting that abnormalities (a) occur early in the disease, (b) do not increase as the disease runs its course and (c) tend to persist for at least several weeks.

The electrocardiographic findings were analyzed as follows:

*Arrhythmias.* Sinus tachycardia was observed in 9 cases (4.0%) and extrasystoles in 2 cases (0.9%). In the absence of additional evidence of cardiac involvement these findings may be disregarded.

*P-waves.* The P waves were abnormally high and peaked in 6 cases (2.7%); notching and widening were not present. This abnormality may have been due to a toxic effect of the disease.

*P-R Interval.* Abnormal prolongation of the P-R interval beyond that expected for the patient's age and heart rate (4) occurred in 7 cases (3.1%), and may represent true conduction defects.

*QRS Complex.* Abnormal slurring of the QRS complex in one case probably signifies a myocardial abnormality. Unexplained left axis deviation was noted in 8 children (3.5%), and must be regarded as abnormal. In 5 cases (2.2%) right axis deviation was observed in addition to other abnormalities.

*RST Segment.* Abnormal RST deviation occurred in 5 cases (2.2%), and is reasonable evidence of a myocardial disorder.

*T waves.* The T waves were abnormally flattened, diphasic or inverted in 8 cases (3.5%) and represents myocardial derangement.

The prevalence of the disease in the summer months and treatment with hot packs raise the question of the influence of electrolytic imbalance upon the electrocardiogram. This possibility is

excluded on the basis that the fluid balance of the patients was maintained.

Prostigmine and atropine were commonly employed but in only 1 of the 32 patients with abnormal tracings was there a possible time relationship between the use of the drugs and the abnormalities.

Electrocardiograms were not obtained in the 11 (2.4%) fatal cases. Autopsy findings consisted of subepicardial petechiae, ventricular dilatation, reduced myocardial consistency, interstitial edema, congestion and perivascular and interstitial cellular reaction. As certain of the changes observed represent toxic, degenerative or anoxic effects, with or without inflammatory reaction, one may infer only that myocardial derangement exists, particularly since the electrocardiographic changes are neither uniform nor specific.

The correlation between electrocardiographic abnormalities and severity of infection and the finding of myocardial changes in a high percentage of fatal cases make a thorough study of the cardiovascular system a necessity in all severe cases of poliomyelitis.

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### *Abstract 4*

Protein Metabolism in the Course of Leukemias. Max M. Strumia, M.D.

For proper dosage of irradiation and for the proper management of leukemic patients and patients suffering from malignant granuloma, it is necessary to take in consideration the uric acid level and the nitrogen balance. It has been observed that there is a definite relationship between the amount of uric acid in the blood and the amount of irradiation which a given patient can stand without untowards reactions. It may be generally stated that patients with a blood uric acid level of 4 mg. or less can tolerate fairly large doses without untowards reactions. Patients with 4–7 mg. will tolerate small to moderate doses, or about 40 R units, but patients with 7 mg. of blood uric acid or more must receive minimal doses not exceeding 25 R units in order to avoid severe untowards reactions.

A study of the nitrogen metabolism of patients suffering from leukemias in general and lymphoblastomas in particular, has been made to seek a possible explanation for the great difference in the severity of the course of the disease in patients who have apparently identical hematological manifestations. In other words, it has been noted that of two patients with chronic lymphatic leukemia with approximately the same degree of lymphomatous infiltration, bone marrow infiltration and circulating blood picture and treated with comparable x-ray doses, one may respond promptly with a sustained arrest or modification of the disease whereas another will show little change. This is particularly true of the degree of anemia. The degree of anemia has been generally attributed to the amount of bone marrow infiltration. However, when confirmation of this is sought in bone marrow studies, no constant relationship can be established.

The preliminary studies so far conducted of the nitrogenous metabolism have shown that:

(1) The amount of urinary nitrogen varies considerably in patients of leukemia, but is generally greater than in normal individuals, and is roughly parallel to the severity of the course of the disease;

(2) That when patients with a high nitrogenous loss are placed on a high protein diet, an amelioration of the anemia and of the patient's general condition usually follows;

(3) That patients receiving adequate x-ray therapy generally have a lower nitrogenous loss than patients not receiving an adequate x-ray therapy;

(4) That patients habitually in a positive nitrogen balance withstand infections in the course of leukemias better than hypoproteinemic ones.

### *Abstract 5*

Pheochromocytoma of the Adrenal Medulla. Robert L. Mayock, M.D., and Edward Rose, M.D.

The case is reported of a man aged 42 with a pheochromocytoma of the adrenal medulla associated with paroxysmal bouts of hypertension and other phenomena. Various studies were made before the removal of the tumor, during attacks, and between attacks. Further studies were carried out one and five months following the disappearance of symptoms which occurred after

operation. The tumor weighed 42 gms., and contained 72 mgm. of free epinephrine.

The most important changes noted were as follows: 1. marked insensitivity to large amounts (2.0 cc of 1/1000 solution) of subcutaneously injected epinephrine prior to operation. 2. Normal sensitivity to injected epinephrine one and five months after operation. 3. A marked increase in serum potassium during symptom free intervals before operation, with a decrease to subnormal levels during attacks. 4. Increased potassium content of a portion of rectus abdominis muscle removed during operation.

The possible significance of some of these changes is discussed and epinephrine insensitivity is suggested as a possible diagnostic test in suspected cases of functioning tumors of the adrenal medulla.

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# Studies in Chemotherapy of Tuberculosis Including Use of Streptomycin*

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ONE who accepts an invitation to lecture in Philadelphia on any phase of tuberculosis must be intrepid indeed. For many decades the contributions of the Philadelphia men of science to the theoretical and practical problems of tuberculosis have been outstanding and of lasting importance. They have worked long and well and it is with much humility that I venture to recount some of the work Dr. H. Corwin Hinshaw and I have done in our attempts to contribute to the therapy of clinical tuberculosis through the use of specific antibacterial agents.

To be awarded the Alvarenga Prize for 1946 is a high compliment to me personally and to the institution of which I am a part. I want to express to the committee my warmest thanks and appreciation of the recognition your cordial invitation implies.

In the time available for this presentation it will not be possible, nor would it be profitable, to include a review of the entire field of chemotherapy in tuberculosis.[1] To find a substance that would influence favorably the course of this disease has been the objective of countless investigations. Until recently the efforts have been largely in vain. Ehrlich's brilliant success in providing salvarsan for syphilis, and the spectacular effects of the sulfonamides and of penicillin in a long list of infectious diseases were important advances in the struggle of man against his microbial enemies. The triumphs of chemotherapy over a variety of nontuberculous infections have been sufficiently impressive to justify the anticipation that eventually tuberculosis would be curbed by drugs.

The present phase of treatment of tuberculosis by drugs dates from 1938 when Rich and Follis (4) showed by properly conducted experiments on animals, that sulfanilamide was capable of a definite antagonistic action against experimental infections produced by the tubercle bacillus. This observation was of the greatest significance. While it is true that the sulfonamides proved entirely disappointing as specific therapeutic agents in clinical tuberculosis, the results of their use on infected animals were in some instances sufficiently suggestive to indicate that the problem should be re-examined. Subsequent and extensive investigations revealed that several representatives of a group of compounds known as sulfones were strikingly effective in suppressing previously established tuberculosis in the highly susceptible guinea pig (1, 2, 3). As a consequence infections produced by the tubercle bacillus, considered previously to be intractable, were finally shown to

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[1] A recent review of chemotherapy in tuberculosis has been prepared by Feldman (1, 2, 3).

be amenable to the antagonistic action of specific drugs.

The results of the experiments on animals with the sulfones, particularly with promin, diasone and promizole, justified the hope that these substances would be equally effective in clinical tuberculosis. These hopes were not realized. Studies revealed that all of the familiar sulfones have certain definite disadvantages which prevent the acceptance of any of the group as the ultimate chemotherapeutic agent in clinical tuberculosis. All of the sulfones which have been studied produce hemotoxic changes of variable degrees of severity. The potentially toxic character of the sulfones imposes a sharp limitation on the amount of these drugs that can be tolerated safely, and this fact probably accounts for the inability of the sulfones to exert a more nearly complete antagonistic effect against the tubercle bacillus, particularly in human beings.

Ideally the drug of choice for the treatment of tuberculosis should be one which has a high specific bactericidal effect in vivo and yet is devoid of serious toxic potentialities. This is a trite reference to a problem as old as chemotherapy and would not be apropos except for the fact that some progress has been made and that further advances appear likely.

Following the sulfones, the next phase in the recent development of chemotherapy in tuberculosis was concerned with the use of the antibiotic substance known as streptomycin (5). Before I deal with this aspect of our investigations, it is desirable to consider briefly a few of the basic factors that must be recognized if the experimentalist is to approach the problem of chemotherapy of tuberculosis with understanding. Too often investigators have entered this field without an appreciation of the fact that tuberculosis, whether naturally acquired or experimentally induced, differs greatly from most infections that have responded to chemotherapeutic substances. It cannot be overstressed that a thorough understanding of the pathologic and pharmacologic factors inherent to this problem is an indispensable prerequisite to the proper conduct of all chemotherapeutic research. This is especially necessary in tuberculosis in which the elaborate complex pathologic characteristics of the disease constitute unusually formidable obstacles to a successful result.

## IMPORTANT BASIC CONSIDERATIONS

*Significant basic factors.* The factors that must be reckoned with in the search for substances capable of inhibiting, arresting or resolving infections produced by the tubercle bacillus are many. The most important of these will be considered: The first is the character of the lesion. It is obvious that early exudative cellular reactions with a minimal of destruction of tissue, necrosis and repair offer a more promising type of disease for effective chemotherapy than one of long duration in which there is considerable mechanical alteration with massive necrosis and formidable zones of peripheral encapsulation. In the latter situation the investigator is confronted with the question of permeability of the morbid tissue by the therapeutic agent. Desirable as this may be, it is conceivable that a highly potent agent may influence the disease in a favorable manner without necessarily exerting a lethal effect on the tubercle bacilli within the mechanical protection of an encapsulated necrotic focus. If the presence of an antagonistic agent at the periphery of a tuberculous focus inactivates or kills tubercle bacilli that would otherwise establish fresh daughter tubercles or be disseminated to distant situations by the blood stream or by the lymph, a definite favorable effect has been achieved. If the infection can be held in check for an adequate period natural resistance will permit reparative processes to become operative. In most instances this process will be sufficiently effective to control the infection.

If the chemotherapeutic agent is sufficiently diffusible to enter a tuberculous focus, the possible inability of the drug to come into direct contact with tubercle bacilli that are phagocytized by mononuclear cells must be considered. Some evidence indicates that tubercle bacilli within the protection of mononuclear phagocytes are more difficult to eliminate by extraneous agents than are those living extracellularly or those within epithelioid cells. Also of possible significance in the therapeutic effectiveness of a drug is whether or not it is inactivated by proteins in the blood serum.

The peculiar chemical constituency of the tubercle bacillus has frequently been considered a formidable obstacle to successful chemotherapy in tuberculosis. In my opinion this factor has been emphasized in excess of its actual importance. The tubercle bacillus like other living cells becomes vulnerable to any substance that is capable of interfering with its intake of nutrient materials necessary for a healthy bacterial economy. The limitations evident in this attack are those imposed by the tolerance of the animal for the substance used. The list of agents that will kill or inactivate

tubercle bacilli in vivo is large but the toxicity of the vast majority for healthy tissue is so great as to preclude their use therapeutically.

In the critical evaluation of substances proposed for use in treatment of tuberculosis certain factors concerning the experimental procedures should be kept in mind. Although Dr. Hinshaw and I fully recognize the importance of an in vitro test that would yield results consistently in agreement with those obtained by in vivo procedures, until such a test is developed and its reliability established we feel that the in vivo approach is the method of choice in the critical evaluation of new drugs effective against the tubercle bacillus. Perhaps it would be more nearly ideal to use both in vitro and in vivo procedures. Animal experimentation, however, is important before any drug—no matter how promising it may appear in vitro—be used in treating a human being. This position I feel is unassailable.

Several factors should be recognized in the conduct of in vivo experiments designed to separate effective from noneffective drugs. Since these have been discussed in some detail in previous articles (1, 2, 3), it will suffice to list them only briefly at this time. Of much importance is the virulence of the strain of tubercle used to inoculate the experimental animals. A satisfactory strain is one that when injected subcutaneously into guinea pigs in medium to small doses produces typical progressive, disseminated and invariably fatal tuberculosis. In crucial experiments it is essential that treatment be delayed until the infection has become well established. A therapeutic substance that will operate effectively against an experimental tuberculous infection that is morphologically detectable before treatment is started is worthy of clinical trial provided it can be administered with safety to human beings. Before treatment is begun all animals should be tested with tuberculin and any that do not react positively should be eliminated from the experiment. A second tuberculin test should be made when the course of treatment has been completed.

Information regarding the permanency of therapeutic effect is of much importance. This may be obtained by several procedures, the most dependable being to discontinue treatment and kill half of the animals that were treated and keep the rest under observation for several additional months. At necropsy the amount of disease in the two groups will indicate whether or not the infection was actually eliminated as a consequence of treatment or was only suppressed by the bacteriostatic action of the drug.

Any drug that shows promising therapeutic activity against experimental tuberculosis induced by a given strain of tubercle bacilli should be tested also against infections produced by several, preferably recently isolated, strains of both human and bovine types of tubercle bacilli. The results, if comparable to those obtained in the original experiments, will provide valuable information to both the experimentalist and the clinician.

*Essential preclinical requirements of a therapeutic agent for tuberculosis.* I cannot overemphasize the importance of obtaining certain essential information regarding every drug for which clinical trial is contemplated. As mentioned previously, this information can be obtained only by animal experimentation. To proceed without such information may conceivably lead to disaster and most certainly to confusion. The experimentalist has a definite responsibility in this matter and he should be prepared to resist the premature enthusiasm of the adventuresome colleague who may insist on using clinically promising drugs on evidence that is inadequate or that may even be erroneous.

Certain critical requirements for a drug that is being investigated for its possible therapeutic value in tuberculous infections may be listed as follows:

1. The agent should be well tolerated and should not produce serious or irreversible physiologic derangements.

2. The substance should reverse a well-established inoculation tuberculosis, induced by a strain of human tubercle bacilli of standard virulence, from a progressive, destructive process to one that is nonprogressive and will eventually resolve, fibrose or calcify. The obvious consequence of such effects would be the extended longevity of the treated animals.

3. The substance should eliminate or render avirulent tubercle bacilli from the organs of predilection, such as the spleen, lungs and liver, and hence preclude subsequent activity of possible latent infection.

4. The desired results should be obtained within a reasonable period of treatment. In estimating what this interval should be, it must be recalled that the lesions of tuberculosis are slow to heal. Experience suggests that in guinea pigs six months is a reasonable period for such healing.

It may appear to some workers that certain of these requirements are unnecessarily stringent and impractical; yet it is obvious that drugs that meet

these conditions should, theoretically at least, be more likely to succeed clinically than drugs meeting less rigid tests. Man's cupidity and the hope and faith of the sick in the miraculous have through the centuries been responsible for the use of almost any substance in treating tuberculosis, no matter how fantastic it might be. The future approach should be based on facts rather than on fantasy. This is possible only by insisting that no substance be prescribed for a human being unless its relative safety and specificity against the tubercle bacillus have been established by proper animal experimentation. As a matter of fact, it should be accepted as axiomatic that biologic experimentation is an integral and indispensable phase of the investigation of therapeutic drugs.

*Loss of sensitivity of tubercle bacilli.* The practical application of chemotherapy has been complicated by the fact that many disease producing micro-organisms, after exposure to a therapeutic agent may lose their original sensitivity to the drug and become in fact highly resistant. Whether or not tubercle bacilli exposed in vivo to the sulfones acquire drug-fastness is not known. It is known, however, that under certain conditions tubercle bacilli that are highly resistant to streptomycin may be demonstrated.

Since it has been shown that tubercle bacilli having considerable resistance to at least one therapeutic agent do occur, there exists an impelling reason for the search for new and more potent drugs that might accomplish successful chemotherapy as conceived by Ehrlich. This was the chemical sterilization of the living body by a single dose of a specific drug. Although this objective may not be within the realm of possibility so far as tuberculosis is concerned, it would seem desirable to have available for therapeutic use as many effective drugs as possible in order to attack the bacteria that are resistant to one agent by the alternate use of others.

*Comment.* The foregoing discourse constitutes a brief account of the more important basic considerations that should be familiar to the experimentalist who would enter the field of research for a therapeutic agent effective in tuberculosis. It is obvious, of course, that there is much more to the problem than has been set forth here. This is indeed a difficult and complex field of investigation and if substantial advances are to be made the attack on the problem probably can best be made by the co-operative efforts resulting from group research. Successful research in chemotherapy is most likely to be accomplished when the diversified talents and enthusiasms of the chemist, the pharmacologist, the bacteriologist, the experimental pathologist and the clinician are pooled for the attainment of a common purpose.

Future possibilities in this perplexing field of medical science are many. The enormity and the importance of the problem justify adequate financial support, and the efforts of the most competent talent that science affords. There has been established during the past few years sufficient evidence to indicate definitely that successful chemotherapy in clinical tuberculosis is a distinct probability within a relatively short period of time. With the information now available, it is not unlikely that in the relatively near future the clinician will have the choice of several drugs having a high specificity for tuberculous infections. Certainly this particular field of medical therapeutics is pregnant with beneficent possibilities for the tuberculous patient.

## ANTIBIOTICS AS ANTITUBERCULOSIS AGENTS

The existence of substances of microbial origin capable of antibacterial effects was recorded nearly seventy years ago by Pasteur and Joubert (6). They noted that certain air-borne bacteria inhibited the growth of the anthrax bacillus. The medical significance of this phenomenon was apparent to Pasteur and Joubert who wrote "These facts justify the highest hopes for therapeutics." Since the observations of Pasteur and Joubert, many attempts to make direct or indirect use of microbial antagonists in the treatment of infectious diseases have been made.[2] When the age-old importance of tuberculosis is considered, it is not surprising to find that forty-four years before Fleming's first report on penicillin, an attempt was made to obtain therapeutic effects in clinical tuberculosis by antagonistic substances of bacterial origin (7). A review of the literature pertaining to the search for substances of microbial origin that would exert antagonistic influences against tubercle bacilli discloses that many such agents have been found (3). However, due to the difficulties inherent in the production, extraction and purification of antibiotics very few have been subjected to tests adequate to establish their exact value as therapeutic agents. In the majority of instances evidence of antibacterial effects against the tubercle bacillus was limited to the results of in vitro testing only. Very

[2] Florey (8) has contributed an admirable review on the use of micro-organisms in therapeutics.

few of the reported substances have received a crucial test of in vivo application in experimental tuberculosis of animals. An outstanding exception is to be found in the case of streptomycin. This antibiotic has passed the crucial test successfully in animals and is now being produced in quantities sufficient for clinical trials.

Dr. Hinshaw's and my interest in streptomycin dates to April, 1944, a few weeks after the announcement of its discovery by Schatz, Bugie and Waksman (9), when Dr. Waksman placed at our disposal a small quantity of crude streptomycin produced in his own laboratory. It seemed important to study the effect of this substance on experimental tuberculosis because of the report by Schatz and Waksman (10) that the bacillus of tuberculosis was sensitive to streptomycin in vitro. The amount of streptomycin available to us was sufficient to treat only four tuberculous guinea pigs for a brief period. The results obtained were so impressive that we journeyed to New Brunswick, New Jersey, to discuss our observations with Dr. Waksman and to explore with him the means of securing enough streptomycin for a crucial study of the drug in experimental tuberculosis. The co-operation of Merck & Co., Inc., of Rahway, New Jersey, was obtained and we were assured a considerable amount of adequately purified streptomycin. This made it possible to carry out a well-controlled, crucial series of experiments between July, 1944, and January, 1945.[3] These experiments clearly demonstrated the therapeutic possibilities of this remarkable antibiotic and indicated definitely the desirability of trying streptomycin in a few cases of clinical tuberculosis.

## EFFECTIVENESS OF STREPTOMYCIN AGAINST TUBERCLE BACILLI[4]

Streptomycin has shown efficacy in vivo against the experimental infections produced by penicillin-resistant micro-organisms belonging to the genera Salmonella, Pseudomonas, Shigella and Brucella; Pasteurella; Leptospira; Borrelia; Klebsiella and Mycobacterium.

Since the scope of this presentation is restricted to agents effective against tubercle bacilli I will not be concerned at this time with the effect of streptomycin on micro-organisms other than those of the genus Mycobacterium.

*Activity in vitro.*[5] The sensitivity to streptomycin of tubercle bacilli of the human type was first observed by Schatz and Waksman (10). In a study of a considerable number of bacteria belonging to several different genera these workers noted that the human type of tubercle bacilli had a moderate sensitivity to streptomycin. Both bacteriostatic and bactericidal effects were recorded.

Youmans (13) also studied the effect of streptomycin in vitro on the human type of tubercle bacilli. In addition he studied the relation of the number of bacteria to the bacteriostatic action of streptomycin and the influence of plasma on the action of streptomycin in vitro. Five fully virulent strains of tubercle bacilli were utilized. Youmans found that the minimal concentration of streptomycin necessary for bacteriostatic action was somewhere between 0.095 and 0.78 microgram per milliliter. The degree of sensitivity to streptomycin was comparable for all five strains studied. Information obtained more recently by Youmans showed that of a total of fifty-eight strains of tubercle bacilli of the human type studied, growth of 70.8 per cent of the strains was inhibited by less than 1 microgram of streptomycin per milliliter. The remainder of the strains (29.2 per cent) have required more than 1 microgram of streptomycin per milliliter for inhibition of growth. None of the patients from whom the respective strains were obtained were receiving streptomycin when the tubercle bacilli were isolated. This was in approximate agreement with the results of Schatz and Waksman (10). To obtain a bactericidal effect Youmans found that streptomycin in excess of 50 micrograms per milliliter was necessary. Neither the number of bacteria nor the presence of plasma

[3] Dr. Hinshaw and I wish to acknowledge our gratitude to Dr. S. A. Waksman, soil microbiologist, New Jersey Agricultural Experiment Station, New Brunswick, New Jersey, and to Dr. J. M. Carlisle, Dr. D. F. Robertson and Dr. Hans Molitor of Merck & Co., Inc., Rahway, New Jersey, for their continued interest and assistance in furthering our investigations on streptomycin.

[4] For information regarding the nature and certain biologic features of streptomycin the reports by Waksman and his associates (11, 12) may be consulted.

[5] Originally a "unit" was proposed as the quantitative standard of potency for streptomycin. A unit of streptomycin was defined as that quantity necessary to inhibit growth of a certain strain of Escherichia coli in 1 c.c. of nutrient broth or agar. At present the potency of streptomycin is expressed in terms of its equivalent in weight of pure streptomycin base, 1 microgram of the latter being equal to 1 unit in the nomenclature used previously. Chemically pure streptomycin has a potency of approximately 800 units per milligram.

had any significant effect on the bacteriostatic action of the drug.

In incomplete studies, Youmans also has shown that the sensitivity of bovine strains of tubercle bacilli to streptomycin is comparable to the sensitivity of tubercle bacilli of the human type (14). He has found, as Schatz and Waksman reported, that avian tubercle bacilli have a resistance in vitro to streptomycin greatly in excess of that observed in the human and bovine types of tubercle bacilli.

*Activity in vivo.* The ability of streptomycin to exert a definite inhibitory effect against tubercle bacilli in vitro suggested the possibility that this agent would be active also in vivo. Subsequent studies have provided unequivocal proof that this is true.

The results of the first three experiments that my colleagues and I conducted on the effect of streptomycin in experimental tuberculosis have been published previously and need not be given in detail in this presentation (5, 15). However, a brief review of our earlier observations is appropriate in order to establish the evidence on which subsequent clinical studies were based.

Our studies on the use of streptomycin in vivo have been limited to tubercle bacilli of the human and the bovine types. We have not observed the effects of this antibiotic in infections produced by the avian type of tubercle bacilli.

First experiment. In our first experiment with streptomycin the amount of the drug available as mentioned previously permitted treatment of only four guinea pigs. Each animal was inoculated subcutaneously with 0.1 mg. of our stock strain of tubercle bacilli, H37Rv. Treatment of two of the guinea pigs was started immediately and continued daily until the end of the experiment. Treatment of the other two animals was delayed for two weeks. Streptomycin was given every three hours during the period from 9 a.m. to 9 p.m. The streptomycin available was exhausted on the fifty-fourth day after infection and the four treated animals were killed. Seven untreated animals which had been inoculated with tubercle bacilli at the same time as the treated animals were also killed. The results were striking. The differences in the amounts of tuberculosis in the treated and untreated animals were impressive and suggested that in vivo streptomycin is an antituberculosis agent of considerable potency.

Second experiment. The results of the first experiment made a second experiment imperative. The second experiment was essentially like the first except that sufficient streptomycin was available to utilize a larger number of animals. Twenty guinea pigs were each inoculated subcutaneously with 0.1 mg. of tubercle bacilli. Ten of the animals were not treated and served as controls.

Treatment of six of the animals was started on the day of inoculation and treatment of four was started two weeks later. As one animal in the treated group and one in the untreated group died prematurely, the final results were based on a total of eighteen rather than twenty animals. Streptomycin was administered every six hours. Because of toxic impurities in the streptomycin used during the early phase of treatment in this experiment, it was necessary to vary the dosage somewhat. A more refined product was eventually obtained and in the latter phase of the experiment each animal received a daily dose of 6 mg. of the drug. The experiment was continued for sixty-one days. The results of the second experiment were comparable in every respect to those observed in the first experiment. The disease in the untreated controls was widely disseminated and in most instances destructive. In the treated animals the reverse was true; signs of the disease were absent or barely detectable. Furthermore, there were no significant differences in the effects of therapy in the group that was treated starting on the day of infection and in the group in which the beginning of treatment was delayed.

The results of the first two experiments left no doubt of the ability of streptomycin to suppress consistently and definitely a potentially lethal tuberculous infection in guinea pigs. Additional studies demonstrated that, although the activities of the tubercle bacilli had been inhibited, some of the organisms remained viable. Of much importance, however, was the evidence that streptomycin was well tolerated by guinea pigs. These findings justified a third and crucial experiment.

Third experiment. In the third experiment forty-nine guinea pigs were used. This was many more animals than were utilized in the previous experiments with streptomycin (15). In addition, the experimental conditions in the third experiment were more rigorous in that treatment was delayed for seven weeks after the animals had been infected. Before treatment was started a specimen of the liver for biopsy was obtained from each animal. This was to provide information on the state of the infection prior to treatment so that the information obtained could be compared with the situation in the respective livers when the experiment was com-

pleted. All animals were inoculated with 0.001 mg. of a strain of tubercle bacilli of human type. All animals exhibited a positive reaction to tuberculin on the forty-second day after infection. Biopsies were done forty-eight days after infection and treatment was started on the forty-ninth day. Twenty-five animals were treated with streptomycin; twenty-four were not treated. Each of the twenty-five treated animals received subcutaneously 6 mg. of streptomycin daily, divided into four equal doses, six hours apart. Treatment was continued for 166 consecutive days. The experiment was terminated 215 days after the animals had been infected.

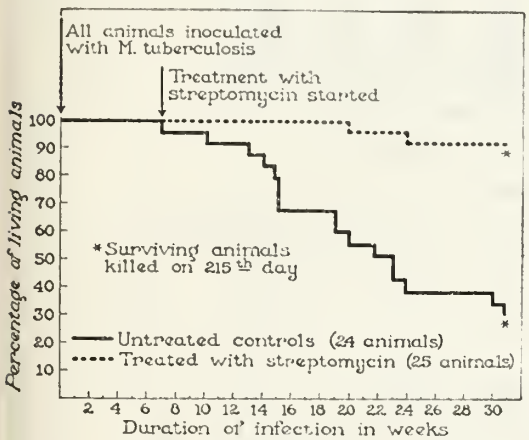


FIG. 1. MORTALITY OF TREATED AND UNTREATED GROUPS OF GUINEA PIGS (THIRD EXPERIMENT).

(By permission of the authors and publisher, from Feldman, W. H., Hinshaw, H. C. and Mann, F. C.: Streptomycin in experimental tuberculosis. Am. Rev. Tuberc. **52:** 269–298 [Oct.] 1945.)

There was a marked difference in the mortality rate of the treated group as compared with that of the untreated group (fig. 1). Although approximately 70 per cent of the controls died during the period of observation, only two (8 per cent) of those that were treated died during this time. Necropsy revealed severe, widely disseminated tuberculosis in nearly all of the untreated controls. Among the animals that had been treated evidence of tuberculosis was either absent or minimal in amount. As a matter of fact, 52 per cent of the animals that had been treated had no discernible tuberculosis either gross or microscopic (fig. 2). Although all animals were sensitive to tuberculin when treatment was begun, nine (39 per cent) of the animals that had received streptomycin and were living failed to react to tuberculin just before the experiment was concluded. In seven of the nine animals in which a negative reaction to tuberculin was recorded no residual virulent tubercle bacilli could be demonstrated in the spleens by subinoculation of normal guinea pigs.

The organs of predilection for the tuberculous lesions of all the animals were examined microscopically. The histologic examination of the tissues of the animals that had received streptomycin provided pertinent information regarding the efficacy of the therapeutic procedure. In only one of these animals was a tuberculous lesion found in the liver; this was a small atrophic nodule. In only one animal was a parenchymal lesion found in the lung. The disease in this animal was represented by a solitary calcified nodule. The spleens of fourteen of the animals were without microscopic evidence of tuberculosis. Tuberculous changes were recognized in the spleens of eleven animals; however, in seven the lesions were calcified, in three the lesions were fibrotic and in one they consisted of epithelioid or hard tubercles. Further impressive evidence of the therapeutic efficacy of streptomycin was the paucity of the disease in the contiguous axillary lymph nodes. In only two of the treated animals was involvement of an axillary lymph node observed. In no instances were residual signs of the disease found in the suprasternal tissues at the site of injection.

The differences in the severity of tuberculosis in the treated and in the untreated groups of animals based on the results of microscopic examination of the tissues of predilection are expressed numerically in Table 1.

The data obtained from our third experiment seem to substantiate certain definite conclusions regarding the therapeutic effects of streptomycin in tuberculosis. Among the more important are the following:

1. Streptomycin, under the conditions imposed, is effective in resolving or suppressing established experimental tuberculosis in guinea pigs.

2. Although capable of undeniable deterrent effects in combating or preventing anatomic changes due to Mycobacterium tuberculosis, streptomycin in most instances exerted a suppressive rather than a sterilizing effect on the infective agent.

3. In more than a third of the treated animals a reversal of a previously demonstrated sensitivity to tuberculin occurred.

4. The unquestionable ability of streptomycin

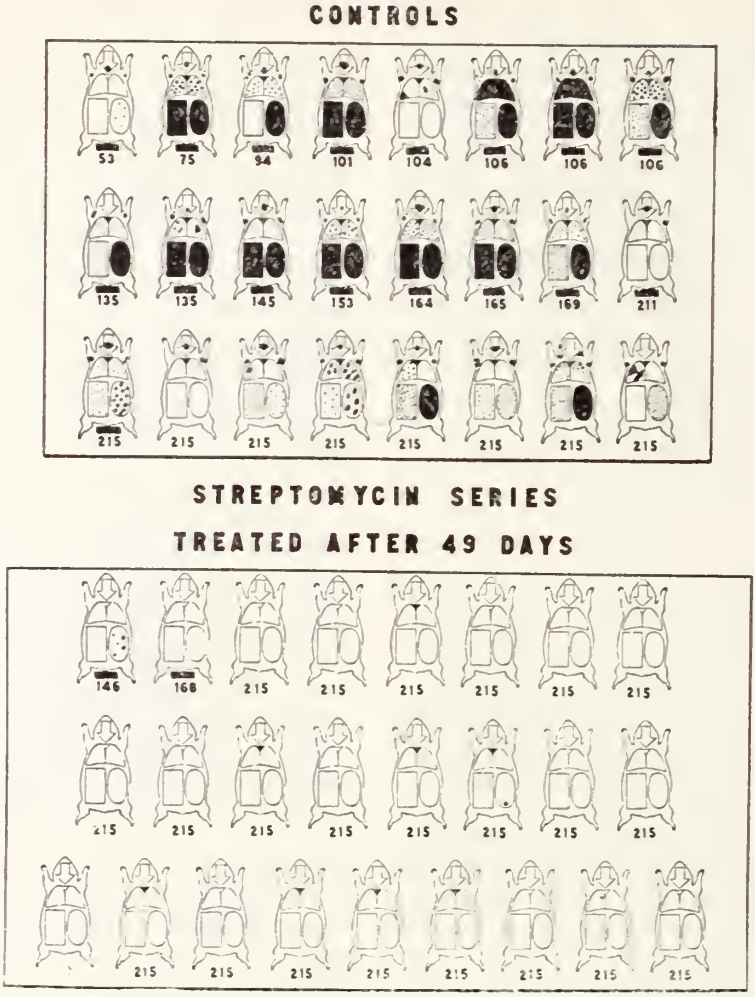


FIG. 2. SCHEMATIC REPRESENTATIONS OF TREATED AND UNTREATED GROUPS OF TUBERCULOUS GUINEA PIGS

Treatment was started forty-nine days after the animals had been infected. Duration of therapy was 166 days. The dissimilarity in the amounts of tuberculosis in the two groups of animals indicates the marked suppressive effects of streptomycin (third experiment). Black indicates heavy infection; stippled, light infection. By permission of the authors and publisher, from Feldman, W. H., Hinshaw, H. C. and Mann, F. C.: Streptomycin in experimental tuberculosis. Am. Rev. Tuberc. **52:** 269–298 [Oct.] 1945.)

TABLE 1

AVERAGE SEVERITY OF TUBERCULOSIS IN DIFFERENT ANATOMIC SITUATIONS EXPRESSED NUMERICALLY

Data based on the histopathologic characteristics of the tissues indicated (experiment 3)

| Group | Animals | Spleen (maximum 35) | Lungs (maximum 30*) | Liver (maximum 25) | Site of inoculation (maximum 10†) | Average index of infection (maximum 100) |
|---|---|---|---|---|---|---|
| Controls (untreated) | 24 | 28.00 | 24.1 | 18.30 | 10.00 | 80.4 |
| Treated | 25 | 0.52 | 0.6 | 0.04 | 0.08 | 1.24 |

* Includes involvement of tracheobronchial lymph nodes when no lesions were found in the lungs.

† Includes contiguous lymph nodes.

to reverse the potentially lethal course of inoculation tuberculosis in guinea pigs, and the relatively low toxicity and corresponding safety of purified streptomycin satisfy the prerequisites of a chemotherapeutic agent worthy of a clinical trial.

Fourth experiment (3). The original observations on the ability of streptomycin to exert a favorable influence on experimental tuberculosis were made on infections established by laboratory stock strains of tubercle bacilli. The clinical importance of information regarding the in vivo efficacy of streptomycin against previously uncultured strains of tubercle bacilli obtained directly from tuberculous patients seemed obvious.

To obtain information regarding the ability of streptomycin to combat successfully infections induced by several recently isolated strains of tubercle bacilli, ten studies were conducted. The inoculums were prepared by using seven strains of tubercle bacilli obtained by gastric aspirations from seven patients who had severe, progressive pulmonary tuberculosis. The tubercle bacilli used in the seven inoculums were the first isolated in these seven cases. In addition, inoculums were prepared from two strains of bovine type of tubercle bacilli (one was the well-known Ravenel strain) and, for comparison, the tenth inoculum was prepared from the laboratory stock strain H37Rv. Ten groups of fourteen guinea pigs each were provided. Each of the fourteen guinea pigs in one group were inoculated subcutaneously with 0.1 mg. of one of these strains of tubercle bacilli. Two weeks later treatment with 6 mg. of streptomycin daily given in four equal doses six hours apart was started for eight animals in each group of fourteen. Treatment was continued for fifty-four days. This experiment was terminated on the sixty-eighth day after infection.

Evidence that streptomycin had exerted a deterrent effect in each of the ten groups of animals was conspicuous. The marked dissimilarity in the gross appearance of the untreated controls and of the treated animals in all groups at the time of necropsy provided convincing evidence of the effect of treatment. Proof of the marked virulence of the respective strains was unequivocal. In most instances the disease in the untreated controls had affected the spleen, liver and lungs extensively. In addition, there was striking tuberculous involvement of the lymph nodes contiguous to the site of inoculation. The initial focus of infection in the tissues at the site of inoculation had persisted and progressed. Open ulceration commonly was present.

During the course of therapy some of the animals died. Among the animals in the respective groups that were treated for fourteen days or longer little evidence of tuberculosis was observed grossly. The absence of both gross and microscopic lesions of tubersulosis in 54 per cent of the seventy-two animals that had received streptomycin for two weeks or longer was impressive. The tuberculosis in the remaining 46 per cent of the treated animals was for the most part minimal.

A summary of the average amount of tuberculosis in each of the ten groups of treated and untreated animals expressed graphically on the basis of data obtained from a microscopic examination of the tissues of predilection is given in figure 3.

The information obtained from this experiment indicates that streptomycin was equally successful in suppressing the infection produced by the seven recently isolated strains of human tubercle bacilli, the Ravenel strain of bovine tubercle bacilli and the laboratory stock strain, H37Rv. The infection produced by the other bovine strain of tubercle bacilli appeared microscopically to be somewhat more resistant than the other nine strains to the suppressive action of streptomycin. However, even in the group of guinea pigs inoculated with this strain and treated with streptomycin the lesions found at necropsy were microscopic in size and non-necrotizing in character and did not reveal evidence of progression.

Although the number of different strains tested in this experiment was small, the evidence indicative of the favorable effect of streptomycin against all of the strains is clear and unmistakable. In vivo sensitivity of mammalian tubercle bacilli to streptomycin is definitely not strain specific. This is in accordance with the results of in vitro studies by Youmans.

Fifth experiment (3). Although my colleagues and I have treated several hundred tuberculous guinea pigs with streptomycin, as yet we do not know precisely what the optimal dose is or how frequently the drug should be administered to achieve maximal therapeutic results. The dose schedule which we have followed has evolved more or less empirically. It is our impression that the therapeutic index of streptomycin for tuberculosis in guinea pigs is so high that considerable variation in dosage is possible without serious prejudice to the therapeutic result.

Of much practical importance in the treatment with streptomycin is the problem of frequency of administration of the drug. Although streptomycin is excreted rapidly, an effective concentration in the blood may be readily maintained by frequent administration. At present we do not know whether a high concentration of the drug in the blood is actually therapeutically more effective than a relatively low concentration.

that the disease was recognizable on gross examination of the tissues of all of these animals. The infection had disseminated in most instances to the spleen, liver and lungs and was definitely progressive. These findings suggested the presence of well-established tuberculosis in all of the animals in the experiment.

On the same day that the aforementioned animals were killed, forty of the remaining fifty-four

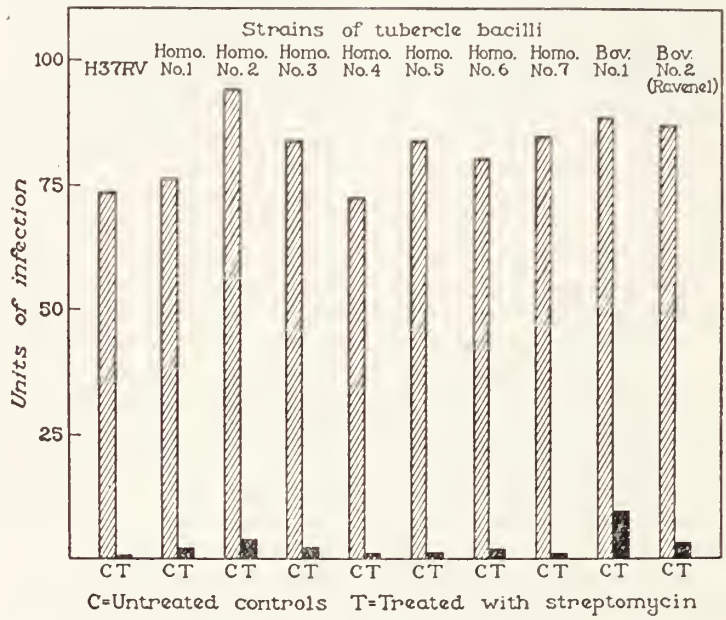


Fig. 3. Comparative Amounts of Residual Tuberculosis Expressed Graphically in Ten Groups of Treated and Untreated Guinea Pigs

The inoculums represented ten different strains of mammalian tubercle bacilli; eight of the human type and two of the bovine type. Treatment with streptomycin was started on the fourteenth day after infection and was continued for fifty-four days (fourth experiment). (By permission of the author and publisher, from Feldman, W. H.: The chemotherapy of tuberculosis including the use of streptomycin; the effect on tuberculosis of antagonistic substances of microbial origin with particular reference to streptomycin. J. Roy. Inst. Pub. Health & Hyg. (3).

In most of our work on experimental tuberculosis the drug has been administered daily at intervals of six hours. To determine whether the therapeutic effectiveness of streptomycin would be markedly influenced by less frequent administration of the drug, a fifth experiment was done.

Sixty-four guinea pigs were each inoculated subcutaneously with 0.1 mg. of human type of tubercle bacilli, strain H37Rv. Twenty-three days later, and before any of the animals were treated, ten of the infected animals were killed to determine the extent of the tuberculosis present. It was found infected guinea pigs were divided into four groups of ten animals each. These four groups were treated with streptomycin. The fourteen remaining animals were the untreated controls.

The respective animals in each of the four groups of treated animals received streptomycin as follows: group 1 received 2 mg. four times daily; group 2, 4 mg. two times daily; group 3, 8 mg. once daily and group 4, 4 mg. four times daily every other week. The total dosage for each animal in all of the treated groups was the same. The duration of the

experiment was eighty-three days. The period of treatment was sixty days.

The results of this experiment showed that in the control group severe and widely disseminated destructive tuberculosis developed. This was apparently responsible for the death of 50 per cent of the untreated animals during the period of observation. In the treated groups the therapeutic effects of streptomycin were unmistakable. The efficacy of the drug was essentially equal in each of the four groups. Consequently, there was no evidence that in tuberculous guinea pigs streptomycin, to be effective, must be administered every six hours. The fact that streptomycin was effective even when given every other week may be of some clinical significance.[6]

From the results of this experiment we concluded that in the treatment of tuberculous guinea pigs with streptomycin frequent administration of the drug was not essential. Consequently, we intend in our future work with animals to give the drug twice daily at twelve hour intervals.

Sixth experiment (3). The most convincing evidence that I have observed regarding the sensitivity of the human type of tubercle bacilli to streptomycin in vivo and the high specificity of this antibiotic agent for these micro-organisms is found in an experiment which at the time of writing has not been terminated. Because of the incompleteness of our observations this experiment will be referred to only briefly.

Twenty-four guinea pigs were each inoculated intravenously with 1 mg. (moist weight) of our laboratory stock strain of tubercle bacilli (H37Rv). Twelve of the animals were not treated and all of these died of generalized tuberculosis after an average survival time of nineteen days. The remaining twelve animals were divided into two groups of six animals each. One group was treated with streptomycin; treatment was begun on the day the animals were infected. Treatment was stopped sixty days later. Except for one animal that died on the second day after infection the animals in this group continued to be well until some time after treatment was discontinued. Eventually the remaining five animals died. The duration of infection before death for each of the five guinea pigs was as follows: eighty-four, eighty-six, 179 and two lived for 193 days, respectively.

The severity of tuberculosis observed at necropsy in the five animals varied. In three the disease was severe and widely disseminated, while in the other two animals gross signs of tuberculosis were not observed. These guinea pigs had died on the eighty-fourth and on the eighty-sixth days after infection respectively. The average survival time for the five animals that were treated for sixty days was 147 days compared to the average survival time of nineteen days for the untreated controls.

Treatment of the animals in the second group was started four days after inoculation with tubercle bacilli. Treatment was continuous for 225 days, at which time all of the animals in the group, except one, were living and are still living at the time of writing, 240 days after the animals had been inoculated with tubercle bacilli. The one animal that died had severe tuberculosis in the lungs; no gross lesions were observed in the liver or spleen of this animal. On several occasions during the course of the experiments the treated animals were tested for sensitivity to tuberculin. All tests gave positive results.

This experiment, while not yet completed, has demonstrated dramatically the potency of the suppressive action of streptomycin on tubercle bacilli of the human type under extremely formidable conditions. Not only was the dose of infective inoculum excessively large but, in addition, the bacteria were introduced by the method (intravenous administration) most likely to produce a rapidly fulminating infection. We know of no other agent that would be as effective as streptomycin under similar exacting circumstances.[7]

### TOXICITY OF STREPTOMYCIN

Our rather extensive experience with streptomycin leads us to believe that this antibiotic in its purified state has a very low toxic potential in doses sufficient for therapeutic results. In our third experiment, although my colleagues and I treated each of twenty-three guinea pigs with 6 mg. of streptomycin daily for 166 consecutive days, we observed no signs that the drug was poorly tolerated. As a

[6] A considerable number of animals in the respective groups treated with streptomycin died prematurely. At necropsy the abdomen in all instances was the site of recent massive hemorrhage. Evidence obtained subsequently indicates that the hemorrhage was due to improper restraint of the animals during the injection of streptomycin.

[7] Youmans and McCarter (16) found streptomycin to be effective in suppressing tuberculosis in mice previously inoculated intravenously with 0.1 mg. of human type of tubercle bacilli.

matter of fact, the animals that received streptomycin maintained a normal rate of growth during the period of treatment and gained an average of 250 gm. while receiving the drug. Of some importance is the further fact that no signs of damage to tissue were found on microscopic examination of the lungs, liver, spleen, kidneys and adrenal glands. Our observation that streptomycin is well tolerated by guinea pigs agrees with the findings of Molitor and his associates and with those of Smith and McClosky (17). In some animals, particularly monkeys and dogs, definite signs of toxicity have been observed. Evidence of toxicity in these animals consisted of transient anemia, mild to severe proteinuria and casts and blood cells in the urine. Dogs receiving streptomycin also manifest signs of disturbances of the vestibular apparatus with possibly decreased auditory acuity. Disturbances of fat metabolism in the liver and kidneys of monkeys and dogs occur. In the monkey these changes are reversible.

Although Molitor and his group (18) stated that "streptomycin . . . appears to be one of the least toxic chemotherapeutic agents," they quite properly voiced a precautionary note regarding the clinical use of streptomycin. Emphasizing that there is a considerable difference in the manner in which different species of animals tolerate this drug, these workers expressed the belief that it would be advisable to observe closely the renal and hepatic function of human beings receiving large doses of streptomycin for prolonged periods.

### ACQUIRED RESISTANCE TO STREPTOMYCIN

The development by tubercle bacilli of resistance to streptomycin in guinea pigs treated with this drug has not been observed up to the present time in my laboratory. The sensitivity to streptomycin of a considerable number of tubercle bacilli isolated from the tissues of guinea pigs treated with streptomycin for variable periods has been assayed. The strain of tubercle bacilli used to infect the guinea pigs was, in all except the fourth experiment, H37Rv. No significant change in the sensitivity to streptomycin was recorded.

In view of Youmans' observation that in strain H37Rv increased resistance to streptomycin developed readily in vitro, our findings appear to be of unusual interest. Is it possible that certain conditions favorable to, or necessary for, the development of increased resistance to streptomycin are not present in guinea pigs?

In clinical work with streptomycin the question of "drug fastness" has been considered and some data have been obtained which were the subject of a preliminary report (19)[8]. The observations were made in vitro on twelve strains of tubercle bacilli isolated from a like number of patients before and after treatment with streptomycin. The tests of sensitivity disclosed that eight of the twelve strains had acquired, during treatment, a marked resistance to streptomycin. In seven of the eight strains the resistance had increased 500 to 1,000 fold. When two additional strains of tubercle bacilli, one a hyman type (H37Rv) and one an avian type, were exposed to streptomycin in vitro resistance increased more than 1,000 fold.

These studies, while not extensive, demonstrate that tubercle bacilli, like various other bacteria, do acquire an increased resistance to streptomycin. What the significance of this may be in the use of streptomycin in clinical tuberculosis is uncertain. If one accepts the analogy provided by the development in vivo of drug resistant bacteria exposed to the sulfonamides and to penicillin, the acquired resistance to streptomycin of tubercle bacilli becomes an obstacle to the complete realization of the therapeutic possibilities of this drug.

Seventh experiment. To obtain information regarding the ability of streptomycin to exert a suppressive effect on experimental tuberculosis induced by a highly resistant strain of tubercle bacilli, the following study was done. Two cultures of tubercle bacilli which had been obtained from the same tuberculous patient were utilized. The tubercle bacilli in one culture had been isolated from the gastric contents prior to the beginning of treatment with streptomycin. These tubercle bacilli were found to be sensitive to 0.15 micrograms of streptomycin per milliliters of medium. The other culture was obtained from the patient after five months of treatment with streptomycin. More than 2,000 micrograms of streptomycin per milliliter of medium were necessary to exert bacteriostatic action on these tubercle bacilli.

Each culture was subjected concurrently to the same experimental procedures. A group of twenty-eight guinea pigs was inoculated subcutaneously with tubercle bacilli from each culture, the amount of infective inoculum for each animal

[8] Most of the earlier determinations of sensitivity to streptomycin were made by Dr. Guy P. Youmans and associates, Medical School, Northwestern University, Chicago, Illinois.

being 0.1 mg. (moist weight). Twenty days later four animals in each group were killed to determine the extent of the disease. In all instances widespread dissemination of the infection had occurred which was recognizable grossly as miliary foci throughout the lungs, liver and spleen. The disease was comparable in both groups and indicated definitely the pathogenicity of the tubercle bacilli in both cultures and suggested that the infection had developed to a comparable degree in the rest of the animals in the two groups.

On the twentieth day after infection, treatment of ten animals in each group was started. The remainder of the animals, fourteen in each group, were the untreated controls. Each of the animals that was treated received 1.5 mg. of streptomycin subcutaneously four times daily. The experiment continued for 166 days after infection. The duration of treatment was 146 days.

The results of this study may be summarized briefly as follows: The last of the untreated controls, inoculated with the tubercle bacilli which were sensitive to streptomycin, died 114 days after infection. All of the untreated animals had extensive tuberculosis. Of the ten guinea pigs inoculated with the sensitive tubercle bacilli and treated with streptomycin twenty days later, only two died. At necropsy there were no gross signs of tuberculosis in these two animals. Six of the eight treated animals that survived the duration of the experiment (166 days) were without gross lesions of tuberculosis at necropsy. The remaining two had moderate to extensive tuberculosis when killed for necropsy. The results of this phase of the experiment indicated that streptomycin had exerted the expected antagonistic effect on a tuberculous infection induced by a human strain of tubercle bacilli which had the usual sensitivity to streptomycin inherent to most strains prior to exposure to the drug.

All of the untreated controls inoculated with the resistant tubercle bacilli were dead 164 days after being infected. All had severe tuberculosis sufficient to account for death. Of the ten guinea pigs that were treated with streptomycin all but two had died during the 166 days of observation. Each of the ten animals in the treated group had lesions of generalized tuberculosis comparable in severity and extent to that which was found in the untreated controls.

The results of this experiment clearly demonstrated the failure to obtain a therapeutic effect with streptomycin in guinea pigs infected with tubercle bacilli that were highly resistant to streptomycin. This result was in marked contrast to the therapeutic efficacy of streptomycin in suppressing a comparable infection induced by tubercle bacilli from the same source before the patient had received streptomycin.[9]

The clinical significance of the results of this experiment are not entirely evident. The patient from whom the cultures were obtained responded satisfactorily to streptomycin therapy according to Hinshaw. Although the tubercle bacilli obtained from the patient at the end of the period of treatment were highly resistant to in vitro and in vivo tests for sensitivity to streptomycin, the disease apparently became stabilized and there has been no reactivation eight months after streptomycin therapy was stopped. Specimens of gastric lavage obtained four, five and six months respectively after streptomycin therapy was discontinued failed to produce tuberculosis in guinea pigs.

About all that one is justified in concluding from this seventh experiment is that in the guinea pig streptomycin is not therapeutically effective if the tuberculous disease is induced by a highly resistant strain of tubercle bacilli. Essentially similar results have been obtained by Youmans (14) in experimental tuberculosis of mice induced by streptomycin resistant strains of tubercle bacilli.

The limited clinical experience with streptomycin in tuberculosis has provided some definite evidence that there are limitations to the duration of therapeutic effects in instances in which the tubercle bacilli develop a resistance to streptomycin. In cases of severe disease in which acquired resistance to streptomycin persists even after the administration of the drug has been stopped, resumption of streptomycin therapy is of doubtful value. There are, however, some data to indicate that the resistance of tubercle bacilli, acquired during a course of treatment with streptomycin, may not be permanent in all instances and that resumption of streptomycin therapy in cases in which the resistance is not permanent may be expected to have therapeutic value.

In view of the incompleteness of the information regarding the exact significance of acquired resistance of tubercle bacilli to streptomycin in clinical tuberculosis, final conclusions regarding the relationship of this phenomenon to the therapeutic potential of the drug must be deferred. That

[9] This experiment has not been completed and will be reported in detail elsewhere.

tubercle bacilli have become markedly resistant to streptomycin should be recognized by all who use this drug clinically. Frequent bacteriologic assays to determine sensitivity after treatment has begun are essential if streptomycin therapy is to yield the maximal beneficent effects. Fortunately in properly selected cases, favorable effects of streptomycin therapy are usually realized before the tubercle bacilli acquire sufficient resistance to the drug to repel its suppressive action.

### STREPTOMYCIN IN CLINICAL TUBERCULOSIS[10]

The ultimate evaluation of streptomycin in clinical tuberculosis will be difficult and long delayed. Possibilities for errors in judgment are many and much more research will be necessary before the exact value of streptomycin in tuberculosis therapy is established. For the past two years my associate, Dr. H. Corwin Hinshaw of the Mayo Clinic, has been investigating the clinical effect of streptomycin in a variety of tuberculous conditions. The number of cases studied has not been adequate nor have they been observed sufficiently long to warrant more than tentative conclusions at this time. However, it is possible to report that certain favorable clinical trends which are fairly consistent have been observed. This encourages us to believe that the results of the experiments on animals which have been described previously may find actual application in medical practice.

It has been possible for him to treat with streptomycin 100 tuberculous patients during the past two years (Table 2). Those patients have been selected with great care. Painstaking effort has been made to exclude any patient who might be expected to show improvement unaided by drug therapy. The difficulty of appraising specific therapeutic effects in an unpredictable disease like tuberculosis because of the possibility of spontaneous improvement in many cases is well understood.

TABLE 2

TUBERCULOSIS TREATED WITH STREPTOMYCIN: SUMMARY OF 100 CASES*†

| Type of case | Number | Remarks |
|---|---|---|
| Miliary tuberculosis and tuberculous meningitis | 12 | Remission of symptoms and findings. Ultimate results uncertain |
| Nonsurgical pulmonary tuberculosis of adults | 32 | Lesions stabilized or improved during treatmen |
| Tuberculous empyema | 7 | Streptomycin given by intrapleural route in effective |
| Tuberculous fistulas | 15 | Uniformly satisfactory response. Recurrence due to inadequate treatment (?) |
| Genito-urinary tuberculosis | 15 | Palliative results good. Disease not eradicate |
| Ulcerating tuberculous lesions of respiratory tract | 7 | Laryngeal, tracheobronchial, and so forth. Prompt healing of ulcers |
| Tuberculosis of bones and joints | 5 | Promising, but not adequately studied |
| Surgical pulmonary tuberculosis | 7 | Promising possibilities |
| Miscellaneous types of tuberculosis | 11 | Of skin, eye, peritoneum, and so forth Worthy of further trial |

* Data kindly supplied by Dr. H. Corwin Hinshaw.

† Eleven patients had tuberculosis of more than one type or location.

Most of the patients selected for treatment have been those afflicted with what were considered intractable forms of tuberculosis. During a pre-treatment period of observation the disease in each case showed unmistakable signs of progression. Within a few weeks after the beginning of treatment the tuberculous process in a majority of the cases was sufficiently altered to cause at least its temporary arrest.

In some types of tuberculosis, especially tuberculous draining sinuses, in which healing trends have been definitely apparent during the administration of the drug, there has been a tendency in some cases for the disease process to become reactivated when

[10] Preliminary reports on the use of streptomycin in clinical tuberculosis have been published by Hinshaw and Feldman (20, 21). A more recent report pertaining to the clinical use of streptomycin in the treatment of 100 cases has been prepared for publication (22).

treatment was discontinued. This recrudescence was reason for discouragement when it was first observed. However, when it was noted that on the resumption of treatment, the disease again responded favorably, this fact was recognized as further evidence of at least a temporary suppressive effect of streptomycin on the tuberculous infection. In some instances the reactivation of the disease could be attributed to inadequate dosage or to treatment for too brief a period. In recent months the clinical results have been superior to those noted during the earlier phase of the clinical studies. These improved results may be due to the fact that the streptomycin used has been more refined and the larger amount provided has permitted treatment for longer periods than was possible previously.

Suggestive evidence of the ability of streptomycin to promote a reversal of the progressive course of tuberculous lesions was established by the histologic examination of material from several fatal human cases (22). The material was from cases of either miliary or meningeal tuberculosis or a combination of the two forms of the disease. The duration of treatment varied from five days to many months. The dose of streptomycin was from 1 to 4 gm. daily.

Although these patients died, treatment in most instances extended the duration of life considerably beyond that of patients who had similar lesions, not treated with streptomycin. Definite morphologic signs of the effect of treatment were observed at necropsy in the lungs, liver and meninges. These signs were (1) contraction of the lesions, (2) disappearance of epithelioid elements, (3) reduction or absence of caseation, (4) fibrosis and hyalinization and (5) encapsulation of foci.

It is important to emphasize the limitations of streptomycin in the treatment of tuberculosis. Sharp distinctions should be drawn between a chemotherapeutic drug which is bactericidal in vivo and streptomycin, which appears to be largely bacteriostatic. We have chosen to use the term "suppressive action" to describe the effect of streptomycin in clinical tuberculosis. The usefulness of streptomycin in clinical tuberculosis is apparently dependent on a continuation of the suppressive action of the drug for a long period.

## FINAL COMMENT

In this lecture experimental evidence has been reviewed which, I believe, establishes definitely that tuberculosis is vulnerable to a chemotherapeutic attack. No longer must infections by the tubercle bacillus be considered as beyond the effective range of drug therapy. The future possibilities for obtaining a highly potent specific substance or a combination of substances are promising.[11] Whether the agent of choice eventually proves to be a synthetic substance or a substance of microbial origin is problematic. Streptomycin is not the first nor is it likely to be the last of the agents that have the ability to affect the course of experimental and clinical tuberculosis in a favorable manner.

The future possibilities for new and more potent antibiotics are impressive. Waksman (23) stated that "the utilization of the activities of antagonistic micro-organisms for the control of human and animal disease has only begun."[12]

When the complex character of the morbid reaction to the tubercle bacillus is considered, it is obvious that a complete chemotherapeutic triumph over tuberculosis can be accomplished only by a substance capable of acting effectively under most formidable circumstances. However, the factors to be reckoned with are not insurmountable and should not deter further efforts to find more effective agents nor do they necessarily imply that agents of even limited effectiveness are unworthy of extensive experimentation.

Although the drugs at present known to be effective in modifying tuberculous infections favorably are predominantly bacteriostatic rather than bactericidal in action, this fact does not invalidate their therapeutic value. As Dubos (24) pointed out, "to interrupt the pathogenic career of an infective agent . . . it is not necessary to kill the invading cell, but only to block one step in its metabolic path by some specific inhibitor."

My colleagues and I view the present status and future possibilities of chemotherapy in clinical tuberculosis with hopeful enthusiasm, being ever mindful of the fact that neither streptomycin nor any of the other known substances that have proved effective in experimental animals can fully qualify as the long awaited curative drug. Our

[11] Smith and McClosky (17) observed what they believed to be a synergistic action in tuberculous guinea pigs subjected to the combined effects of promin and streptomycin. The results indicated that the combined treatment was more effective than was treatment with either substance alone.

[12] According to Waksman (23), 20 to 40 per cent of all the actinomycetes are known to be capable of producing antibiotic substances; this potentially rich repository remains largely unexplored.

greatest concern throughout the several years of our investigations has been and is the constant danger that the tuberculous patient may abandon or delay conventional forms of treatment in favor of some inadequately tried drug that has been the subject of premature enthusiasm. The following statement by the late Dr. Paul Lewis (25) deserves repetition and emphasis: "Certainly it will be a most unfortunate thing for the progress of tuberculosis research if every substance showing interesting properties in the laboratory is immediately rushed to the clinic regardless of consequences. In this situation patience is to be taken more than usually as an evidence of virtue." While the experimental results up to the present time are suggestive of the future possibilities of the chemotherapeutic attack on infections produced by the tubercle bacillus, they definitely do not warrant the conclusion that the ideal chemotherapeutic agent for clinical tuberculosis has been found.

Until more potent substances are available for chemotherapy in tuberculosis those concerned with the control of this disease should not neglect the application of other and effective means of attacking the problem. Early diagnosis by mass surveys, segregation of contagious patients and adequate care and treatment in a sanatorium are the indispensable features of an effective program of tuberculosis control. A highly effective chemotherapeutic agent to supplement such a program would provide reason for the belief that eventually tuberculosis might become a rare disease.

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# Experiences with Primary Atypical Pneumonia in World War II*

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RECOGNITION of an unusual form of pulmonary infection in which common pathogenic bacteria did not appear to play a causative role was first made in 1934 with the almost simultaneous reports of Gallagher and of Bowen. The former described the clinical, laboratory and roentgenographic features of 16 cases of "bronchopneumonia" occurring in a preparatory school of 350 boys. The benign character of the pulmonary infection was described and the disparity between roentgen and physical signs in the lungs emphasized. Bowen reported the occurrence of a similar group of cases occurring among white troops in Hawaii during 1932 and 1933, and considered the pneumonia to be a complication of influenza. Following the appearance of these early reports, which attracted little attention at first, interest in this clinical entity became accelerated, particularly between 1938 and 1942. During this time the number of reports in the American literature increased greatly, the endemic and epidemic occurrence of cases was described, the clinical and roentgenographic features of the disease further delineated and attempts were made to establish the etiology of the infection. The reports of Allen, Scadding, Reimann and colleagues, Smiley and co-workers, Kneeland and Smetana, Longcope, Murray, and Daniels are but a few of those which enhanced our knowledge of the disease.

During the war years 1941 to 1945, primary atypical pneumonia reached a place of eminence in military medicine because of the large number of troops affected and the resultant loss of manpower. Some idea of the seriousness with which the Army looked upon the disease may be gained from the facts that 1) in December 1941 a Commission was sent to investigate an outbreak of primary atypical pneumonia in a Southern training camp, 2) in March 1942 the disease was made reportable to the Surgeon General as a separate disease entity, distinct from other forms of pneumonia, and 3) continuing investigations bearing on this disease were initiated and carried out in Army camps throughout the war period. The result of this war experience has been that we now know a great deal more about primary atypical pneumonia than we did in 1941, but that large gaps in our knowledge still exist. I should like to discuss some of the epidemiological, clinical and etiological features of this disease in the light of this war experience.

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## EPIDEMIOLOGY

*Occurrence.* During World War II primary atypical pneumonia was widely distributed among troops of the continental United States but was also reported from the various theatres of operation. The full extent of this distribution never will be known because of the lack of uniform diagnostic criteria and the variable frequency with which roentgenographic examinations were made on patients ill with respiratory infections. Both of these factors undoubtedly influenced the number of reported cases. An index of the probable frequency of the disease may be gained from statistics compiled by the Preventive Medicine Service, Office of the Surgeon General, which show that there were approximately 94,000 cases of primary atypical pneumonia among troops in the continental United States alone during the period March 1942 to December 1945. Other cases, occurring prior to the time when the disease was made reportable, plus those from the various Theatres of Operation and the unknown number which undoubtedly escaped detection for lack of radiologic study, would probably raise the total by a sizeable figure. Roughly, the attack rate for atypical pneumonia might be estimated at one per cent per year. In the winter of 1942–43 rates

as high as 4 per cent were observed among recruits during the first 8 weeks of training.

The endemic character of the disease was well recognized during the war. At almost any time of year cases could be found on the respiratory wards of Army hospitals. In general, however, the incidence of atypical pneumonia followed the seasonal prevalence of respiratory disease, being greatest in the fall and winter months, but this relationship was by no means constant. At Fort Bragg over a 4 year period, there was a fairly uniform relationship between the incidence of respiratory admissions and atypical pneumonia. The ratio was approximately 10 to 1 not only in groups composed predominantly of new recruits, but also in organizations of seasoned troops which seldom were admitted to hospital in large numbers.

Epidemics of primary atypical pneumonia in Army camps have been rare occurrences. Incidence rates in various camps have varied widely but, in most places where high rates have been reported, investigation has revealed that the increases were more apparent than real and could be explained by improved diagnostic techniques (X-ray) and a heightened, increased awareness of the disease.

*Mode of Transmission.* Little is known about the mode and manner of transmission of atypical pneumonia. Presumably, the disease is acquired by direct contact with an infected person or possibly by the air-borne route. Discharges from the respiratory tract of infected persons and freshly contaminated articles such as handkerchiefs, linen, etc., may be possible sources of infection. The available evidence indicates that food, water, milk, eating utensils and insect vectors are not important factors in the spread of the disease. An interesting and significant hypothesis was advanced by Reimann some years ago, namely, that atypical pneumonia may be but a severe form of a frequently mild epidemic infection of the respiratory tract. Clinical and epidemiological evidence in general, supports this hypothesis but the theory cannot yet be considered as proved.

The incubation period of atypical pneumonia has not clearly been established on the basis of clinical and epidemiological observations. In a few isolated cases the evidence supports the possibility of an incubation period of 1 to 3 weeks.

Little data are available regarding susceptibility and immunity to atypical pneumonia. Presumably, susceptibility to the disease is low if one considers the attack rates in most military installations even during periods of relatively high incidence of infection. On the other hand, susceptibility may be high if "non-pneumonic" forms of atypical pneumonia really exist. Under certain conditions it appears that the factor of dosage may play a primary role rather than unknown innate factors of susceptibility. This is suggested in those individuals who apparently acquire their infection through close and repeated contact with infected patients. These and other questions must await further investigation.

The nature and duration of immunity in atypical pneumonia are complete enigmas. Instances of second attacks have been observed in the Army and no doubt in civilian practice as well, but the frequency with which these occur does not permit even a rough approximation of the length of probable active immunity.

### CLINICAL FEATURES

Clinical descriptions of cases of atypical pneumonia occurring among military personnel have not differed appreciably from those observed in civilians prior to the War. Nevertheless, during the war, diagnostic criteria were sharpened, certain laboratory tests were given thorough appraisal, therapeutic measures were evaluated and the sum total of clinical features of the disease was thoroughly explored.

It is well known that primary atypical pneumonia is a mild or moderately severe respiratory illness in the average patient. The onset is gradual in approximately three-quarters of the cases. The development of local respiratory or constitutional symptoms, or both, marks departure from health, and intensification of symptoms or the discovery of fever usually prompts the patient to seek bed rest and medical care. At some stage of illness all patients experience one or more of several constitutional symptoms of varying degree. Feverishness, chilliness, frontal headache and malaise are the most common symptoms noted. In about 10 per cent of cases a true rigor is observed. Occurring less commonly are anorexia, nausea, vomiting and weakness.

Local symptoms referable to the respiratory tract are present in variable frequency and intensity in all patients. Cough is the most frequent and characteristic feature of atypical pneumonia. It is predominantly dry and often paroxysmal during the first 3 or 4 days of illness and may be accompanied by substernal discomfort, but rarely by true pleural pain. Ultimately the

cough is productive in approximately 80 per cent of the cases. The sputum is mucus, muco-purulent, occasionally frankly purulent, or blood-streaked. Grossly bloody or "prune-juice" sputum is rarely observed. Nasal symptoms (sneezing, coryza, nasal obstruction) and sore throat are each experienced by approximately one-third of the patients. Nasal symptoms are rarely prominent but sore throat may be of moderate severity and an early symptom of illness.

Physical examination in the early stages usually reveals a moderately ill patient with a mild inflammatory reaction of the upper respiratory passages. Cyanosis is the exception rather than the rule. The respiratory rate is normal or only slightly increased and breathing is not labored. Herpes about the lips and nose is rare.

Within the first 24 hours of disease only a third of patients will show physical signs of pulmonary infiltration which consist of subcrepitant, "sticky" moist rales. Other signs of infiltration are usually lacking. The rales are best elicited after a cough and deep breathing. As the disease progresses, the rales become more numerous and may persist for days or weeks. Despite the paucity of physical signs of infiltration early in illness, approximately 80 per cent of cases will show a positive roentgenogram on the first day. This disproportion between physical and roentgenographic signs of infiltration is an almost constant feature of atypical pneumonia.

The roentgenographic signs conform to one or more of several characteristic patterns. The commonest lesion noted is a wedge or fan-shape infiltration with the apex and greatest density at the hilus, becoming less dense yet broader toward the periphery of the lung field. It appears soft and either patchy or homogeneous in character. In some cases, the earliest sign may be peribronchial infiltration at the periphery of the lung without concomitant hilar involvement. This type of infiltration is commonly seen at the lung bases and is best visualised by anterior-oblique films. Diffuse miliary-like lesions may occasionally be observed. These are commonly found in individuals who are severely ill. As with pneumococcal pneumonia the lower lobes are the most frequent site of infiltration (80–90 per cent of cases).

The febrile course in atypical pneumonia is usually remittent, of 3 to 8 days' duration, and terminates by lysis. The pulse and respiratory rates are relatively low during the febrile period.

The total leukocyte and differential counts are usually normal during the acute illness. Biochemical studies of the blood have shown no characteristic features. Two immunological reactions have been extensively studied but each of them is limited to retrospective diagnosis. I refer to the cold hemagglutination test and the agglutination reaction with streptococcus MG. It has been shown that agglutinins for Group O human erythrocytes develop in the convalescent sera of approximately 30 to 50 per cent of cases of atypical pneumonia. Titers of 64 or more, or lower titers showing a rise and subsequent fall, may be considered as strong evidence in favor of a diagnosis of atypical pneumonia when interpreted in conjunction with the clinical findings. The height of the cold hemagglutinin titer is apparently correlated directly with the severity, the height and duration of fever, and the extent of the pulmonary lesion. Cold hemagglutinins, however, have been described in other infections, in certain blood dyscrasias, and in liver disease, as well as in individuals without illness. It is, therefore, not specific for atypical pneumonia, but positive reactions occur with greater frequency in this than in any other condition.

Agglutinins for streptococcus MG, an indifferent streptococcus isolated by Thomas and co-workers at the Rockefeller Institute Hospital, develop in the convalescent sera of from 20 to 75 per cent of patients with atypical pneumonia. The value of this test, however, is limited to retrospective diagnosis. When positive, it may be of aid in confirming the diagnosis; a negative test does not exclude atypical pneumonia.

Bacteriological examination of the sputum reveals flora generally considered to be normal for the respiratory tract. Pneumococci may be found in from 40 to 75 per cent of cases; these are usually of the so-called "higher types." It seems fair to state that in the majority of cases of atypical pneumonia, routine bacteriological study of the sputum yields little information of value. However, examination is to be recommended if bacterial pneumonia is suspected.

Variations in the clinical course of atypical pneumonia may be extreme. The ordinarily benign type of infection is exemplified by the following case summary:

This 19-year-old soldier was admitted to the hospital on April 26, 1943 complaining of feverishness, headache, anorexia, sore throat, hoarseness and cough. For approximately three weeks he had noted a mild respiratory infection, the prin-

cipal symptom of which had been cough. Fever of 102° F. prompted admission. Physical examination showed a mildly ill soldier with slight inflammatory changes of the upper respiratory tract. A few fine subcrepitant rales were audible at the left base. A roentgenogram revealed peribronchial infiltration of the left lower lobe. The acute febrile period lasted three days. Rales were heard for two days. Recovery was complete after a slight exacerbation of symptoms during the second week.

Cultures of the sputum showed *H. Influenzae*, *H. Hemolyticus* and pneumococcus, types 12 and 19. Cold hemagglutinins were not demonstrated in the patient's serum. A rise in titer of influenza antibodies did not occur.

Some individuals are more seriously ill, such as those demonstrated graphically in the following cases:

1. An 18-year-old white soldier was admitted to the Regional Hospital, Fort Bragg on June 8, 1943 with symptoms of 2 days' duration. The present illness began on June 6 with headache, nausea, and vomiting. Later that day he noted chilliness, feverishness and malaise. On June 7 his gastro-intestinal symptoms were improved but other symptoms persisted. On the evening of June 8 when he was found to have a temperature of 101.8° F. he was hospitalized.

The admission roentgenogram, taken on entry to the ward, showed an area of infiltration in the right upper lobe arising from the superior mediastinum. The roentgenographic diagnosis rested between peribronchial pneumonia and tuberculosis. Physical examination revealed temperature 100.2°F., pulse 80, respiration 20. The patient did not appear ill. Nasal discharge and impairment of chest expansion and percussion were the only abnormal physical signs noted. His condition was unchanged during the next 48 hours except for the development of productive cough. On June 10 (5th day) there was an abrupt rise in temperature to 103°F. and he became progressively sicker. Fine and coarse rales first became evident over the right upper lobe on June 12 (7th day). The signs were subsequently heard over the right middle and lower lobes. A portable chest film on June 15 confirmed the clinical evidence of spread within the right lung. On June 16, the 11th day, the temperature fell to normal and thereafter showed no elevation. Physical signs in the lungs were audible through the 25th day. The pneumonic process cleared slowly and only residual infiltration was seen in the roentgenogram taken on July 3 (28th day). Convalescence was uneventful.

Laboratory studies showed a normal leukocyte count and differential formulae during the febrile period. Leukocytosis of 14 thousand without neutrophilia was present during the fourth week. Blood culture on June 9 showed no growth. The sputum showed no significant pathogenic organisms. No acid fast organisms were seen on stained smears of the sputum. The cold hemagglutinin titer on June 21 (16th day) was 512.

*Comment.* Although the location and appearance of the pneumonic lesion suggested a diagnosis of tuberculosis, the clinical course of illness was characteristic of moderately severe primary atypical pneumonia.

2. A 32-year-old female developed dry cough and substernal discomfort on February 22, 1944. The following day these symptoms were still present and physical examination was negative except for the presence of a small amount of pharyngeal exudate. On February 24 she noted chilliness and malaise. Later that day she observed headache and feverishness and the temperature was 101.6° F. On February 25 the temperature reached 102° F. accompanied by sore throat, nasal obstruction, dry cough, chilliness, feverishness and marked fatigue. On February 26 all of the above symptoms became aggravated, the temperature rose to 104° F. and the patient was hospitalized.

A diagnosis of primary atypical pneumonia was made on February 27 with the discovery in roentgenograms of an area of infiltration in the right upper lobe. The clinical course of disease was unusually severe and featured by cyanosis, tachypnea and prostration which accompanied successive involvement of the left upper, right lower and left lower lobes. Oxygen therapy was given for approximately 10 days. Sulfadiazine, 12.5 grams over a period of 60 hours failed to modify the clinical course. On March 3 penicillin therapy was begun and the patient received 1.01 million units intramuscularly at 3 or 4 hourly intervals until March 7. There was an apparent fall in the temperature coincident with the institution of penicillin therapy, but the patient continued to be critically ill. Improvement became evident on March 8, and thereafter convalescence was uninterrupted. The lungs cleared completely and she became symptom-free except for weakness which continued for several weeks after discharge.

The leukocyte count showed a leukopenia with normal differential count. Blood culture on March 3 was sterile. Throat cultures prior to admission yielded normal flora. From a throat washing obtained on March 2 α Streptococcus and Streptococcus MG were cultivated. Seven specimens of sputum obtained between the period of March 2 to 17 yielded the following organisms on one or more cultures: α Streptococcus, Beta hemolytic streptococcus, Group F, and Streptococcus MG. A rise and subsequent fall in cold hemagglutinin titer was demonstrated in samples of convalescent serum. The maximum titers were as follows: March 2, 8; March 8, 256; March 17, 2048; and March 24, 256. Agglutinins for Streptococcus MG were found in a titer of 10 in the serum of February 26 and a titer of 20 on March 17.

Other infections are apparently so mild as to be inapparent and would go unrecognized if routine roentgenography had not been done.

*Complications* are infrequent in atypical pneumonia but may involve the respiratory tract or the cardiovascular and central nervous systems. *Pleuritis* and *pleural* effusion requiring thoracentesis may develop in as much as 5 per cent of cases, but the overall frequency of this complication is much lower. Relapse, delayed resolution, atelectasis, ulcerative tracheobronchitis, lung abscess have been described. Much has been written recently about *bronchiectasis* and *pseudo bronchiectasis* following as a direct result of atypical pneumonia. These are extremely rare in our experience.

The *differential diagnosis* of primary atypical pneumonia involves consideration of other acute diseases of the respiratory tract. These may be grouped into two main classes. First, illnesses with a demonstrable roentgenographic shadow in which the etiologic agents are known. These may be bacteria, viruses, fungi, or rickettsiae. Secondly, illnesses without a positive roentgenogram but with symptoms and/or signs suggestive of atypical pneumonia. In this group, the etiologic agents are unknown but are presumed to be viral in nature.

The bacterial pneumonias ordinarily are not difficult to differentiate from atypical pneumonia. As a group these are characterized by abrupt onset usually with rigor, high fever, grossly bloody sputum, pleurisy, frank signs of consolidation and leukocytosis. A careful anamnesis is of the utmost importance in differentiation. The greatest diagnostic help, however, comes from the laboratory where isolation of the infecting bacterium from sputum or blood is usually readily accomplished.

Pulmonary disease caused by known viruses, e.g., influenza viruses A and B, the psittacosis lymphogranuloma-ornithosis group, and the virus of lymphocytic choriomeningitis will sometimes require differentiation from primary atypical pneumonia. The clinical diagnosis of influenza, with or without pulmonary involvement, is difficult if not impossible. A positive diagnosis can only be made by the use of laboratory procedures such as isolation of the virus in animals or chick embryo, or the demonstration of an increase in specific antibodies in the patient's serum. These laboratory tests are seldom available to the practitioner, but in difficult diagnostic problems use of these procedures is to be recommended.

The rarity of cases of psittacosis or lymphocytic choriomeningitis do not warrant serious consideration in the average patient.

During the war years, coccidioidomycosis assumed considerable military importance. Of the fungus infections it alone need be considered in the differential diagnosis of atypical pneumonia. Isolation of the agent *Coccidioides Immitis*, use of the intradermal coccidioidin skin test, and demonstration of specific antibodies in the patient's serum are all helpful in identifying this infection.

Rickettsial diseases, particularly "Q" fever, clinically may resemble atypical pneumonia. Epidemics of this disease have been reported in this country and recently in troops stationed in the Mediterranean Theatre. "Q" Fever scarcely need be considered in the diagnosis of an isolated case of pneumonia, but in the presence of an outbreak of atypical pneumonia it should always be investigated.

The second class of infections which may be confused with atypical pneumonia is the large group of respiratory diseases of unknown etiology, called by a variety of names such as nasopharyngitis, catarrhal fever, common or undifferentiated acute respiratory disease. This group of diseases accounted for the majority of all respiratory admissions to military hospitals during the war. At Fort Bragg, in the past 3 years, approximately 75 per cent of admissions to the respiratory wards were so classified. Differentiation of these cases from atypical pneumonia can be made by the use of repeated roentgenograms, a critical evaluation of the history, daily examination of the chest and by observation of the clinical course. Recent experimental evidence has indicated that some of

these cases are caused by a filtrable virus which is distinct from that of primary atypical pneumonia.

The majority of patients recover from primary atypical pneumonia without sequellae. Accurate case fatality rates in this disease for the military forces as a whole are not available. From experiences at installations in the continental United States, the over-all fatality rate from atypical pneumonia is probably less than 0.1 per cent. In certain civilian hospitals at some seasons, the fatality rate has been considerably higher.

*Treatment.* Sufficient data have accumulated to indicate that there is no specific form of therapy for primary atypical pneumonia and that use of various sulfonamide drugs or antibiotic agents is seldom necessary or justified. Administration of these agents should be restricted to severely ill patients, or to those whose illnesses are unusually prolonged or complicated by proved secondary bacterial infection and to those in whom the diagnosis is in doubt. The usefulness of convalescent serum or whole blood from normal individuals or convalescent cases has not been established on a firm basis, although Lee reported effective results in 75 per cent of 100 patients in an air-force hospital treated with convalescent serum. It would appear that the difficulties in appraising therapeutic results in a disease as variable as atypical pneumonia are almost insurmountable. If such can be overcome, however, these measures may warrant extensive trial.

## ETIOLOGY

In the remaining time at my disposal I should like to discuss the various attempts which have been made to establish the etiology of primary atypical pneumonia. These have consisted largely of animal and human experimentation. A number of pneumotropic viruses have been isolated from patients in experimental animals by several groups of investigators. But, difficulties of one kind or another have been encountered; namely, inability to propagate the virus successfully, the occurrence of non-specific latent virus infections and the development of spontaneous non-infectious pulmonary lesions in animals. The work of Eaton and his co-workers is the most promising animal experimentation at the present time. These authors have reported the occurrence of pulmonary lesions in cotton rats and hamsters inoculated intranasally with tissue from chick embryos which had been inoculated previously with sputa or lungs from cases of atypical pneumonia. The agent responsible for these lesions was filtrable. Furthermore, convalescent sera from patients with atypical pneumonia prevented the development of lesions by the chick-embryo tissue in the majority of the animals. Recently, on the basis of neutralization tests, Breslow has reported that the virus isolated by Eaton *et al.* was associated with an outbreak of respiratory disease occurring among school children in rural Minnesota.

Extensive animal investigations were undertaken by the Commission on Acute Respiratory Diseases during the war. Throat washings, sputa and blood from more than 60 active cases were inoculated into a variety of domestic and exotic animals. No agents which could be related unequivocally to the human disease were isolated.

In view of these unsuccessful isolation results in animals, attempts were made to transmit the disease to the natural host, man. These studies were made in volunteers, all of whom were conscientious objectors. The plan and the objective of these experiments will become evident as they are described separately.

The first experiment was conducted during the fall of 1943 in a Civilian Public Service Camp administered by the American Friends Service Committee. A preliminary survey of dispensary records at the Camp revealed a normal seasonal prevalence of respiratory diseases in the preceding 12 months and an absence of definite cases of pneumonia. In addition, a roentgenographic survey of the entire Camp personnel of 123 men failed to disclose any cases of pneumonia. A group of fifteen healthy volunteers was segregated from the other campers in a small infirmary. During a pre-inoculation period of 5 days the men were observed daily for evidence of respiratory disease. Three men developed mild afebrile upper respiratory infections during this time. None showed roentgenographic evidence of pulmonary infiltration at this time, or subsequently. Notwithstanding the development of these minor illnesses, inoculations were given to the remaining 12 men. The inocula consisted of a pool of unfiltered throat washings and sputa from seven characteristic cases of atypical pneumonia. The material was sprayed into the nose and pharynx of each volunteer by means of an atomizer and nebulizer, synchronizing the spraying with each inspiration.

Respiratory illnesses of variable clinical patterns developed in 10 of the 12 men inoculated. In two

volunteers the infections were extremely mild and afebrile. Eight cases displayed fever varying from 7 to 22 days after inoculation. In five patients subcrepitant "sticky" rales were audible. In three of these the roentgenogram showed small areas of patchy infiltration in one or more lower lobes, and the symptoms and clinical course were consistent with mild atypical pneumonia. In the remaining two patients the illnesses were characteristic of this infection but radiographic evidence of pulmonary infiltration was lacking. Three of the eight patients displaying fever had no evidence of pneumonia at any time. Cold hemagglutinins in titers of 64, 128, and 256 respectively, were present in the sera of three individuals during the course of illness. Neither influenza antibodies nor agglutinins for the indifferent streptococcus MG of Thomas and Horsfall were present in the sera of any of the volunteers. None of the infections resembled the "common cold." Similar illnesses did not occur in a group of 16 uninoculated men.

The results of this experiment suggested that primary atypical pneumonia was transmissible by means of untreated throat washings and sputa. Interpretation of the results, however, was complicated 1) by the development of illnesses in three of the men prior to inoculation, 2) by the opportunity for cross-infection subsequent to inoculation, and 3) by the failure of any of these with illness to develop striking roentgenographic evidence of pulmonary infiltration. Nevertheless, the experiment was considered sufficiently encouraging to warrant repetition under more rigid conditions of isolation.

Accordingly, second and third experiments were performed during the summer of 1944 in a 75 room hotel. The number of volunteers was increased, rigid quarantine restrictions were employed and the infectivity of filtered as well as untreated and autoclaved respiratory tract secretions was tested.

After a three-week control period of observation three groups of 12 persons each, were inoculated with pooled throat washings and sputa from seven cases of primary atypical pneumonia. One group received untreated material, another group the same material filtered through sintered glass and Seitz filters; the final group received autoclaved material which was shown to be bacteriologically sterile. The inoculations were given in separate rooms in one wing of the hotel during the course of a single day. The technique of inoculation was essentially the same as that employed in the preliminary experiment; namely, the employment of a hand nebulizer and atomizer. In addition, an atomizer, powered by a motor-driven air-pump, was also used. A total inoculum of 10 ml. was administered to each volunteer.

Ten cases of atypical pneumonia, 15 cases of minor respiratory illnesses of undifferentiated type and two illnesses among the professional staff and attendants were observed following these inoculations. Eleven individuals remained well. Examples of mild, moderate and severe forms of atypical pneumonia were seen. Roentgenographic lesions were characteristic of those seen in the naturally-acquired infection. A rise in titer of cold hemagglutinins for Group O human erythrocytes developed in the sera of 8 of the 10 cases of atypical pneumonia. Agglutinins for the indifferent streptococcus MG developed during convalescence in the sera of 2 cases in a maximum titer of 32 from a pre-inoculation titer of $< 8$. No change in titer was detected in the other 8 cases. Cultures of the throat, sputa and throat washings yielded no indications of a direct etiologic relationship between any single organism or group of organisms and atypical pneumonia.

The symptoms, physical signs, course and severity of the minor respiratory illnesses which developed in 15 volunteers, were variable. Constitutional symptoms were noted by 10 of the 15 patients, but symptoms referable to the nose, throat or chest were experienced by all 15. Cough was present in all but one patient and in half of the group the cough was productive. Abnormal lung signs, consisting of transitory fine rales, were present in one patient; exudative pharyngitis was noted in two patients; fever of 99.6°F. or above was present in 4 patients. Cold hemagglutinins in low titer were observed in the serum of one patient. Agglutinins for streptococcus MG were not detected in any of the samples of serum.

Two illnesses occurred in the professional and attending staff following the inoculations. A physician participated actively in the laboratory in the preparation of the inocula, and on the day of inoculation distributed for use all specimens in the inoculation rooms. Twelve days later he developed symptoms and signs of mild atypical pneumonia which was confirmed by roentgenogram. The other individual was an attendant, who assisted in the inoculations and was confined for 5 hours to one of the rooms in which untreated material was being given. Eleven days after this

exposure he developed atypical pneumonia of the left lower lobe.

The following cases illustrate the character of atypical pneumonia produced in this experiment.

1. This patient experienced a mild illness beginning on the 8th day after inoculation. Physical signs of infiltration were audible at both bases. The conventional posterior-anterior film was clear; however, the left and right anterior oblique films disclosed areas of infiltration at both sulci.

2. This patient experienced moderately severe atypical pneumonia beginning in the right hilus and ultimately involving the entire right lung and the left lower lobe. Cold hemagglutinins were present in the serum in a titer of 128.

3. This patient experienced a severe illness. Pneumonic infiltration was diffuse and involved all 5 lobes. He was critically ill and required oxygen therapy for 8 days. Recovery was protracted and complicated by sinusitis, but was ultimately complete. Cold hemagglutinins were present in high titer, 1024, in the patient's serum. Agglutinins for streptococcus MG were likewise present.

4. This case illustrates a mild case of atypical pneumonia complicated by sterile pleural effusion. Pneumonic infiltration was present at both lung bases. Physical and roentgenographic signs of fluid became evident 2 weeks after inoculation. A diagnostic thoracentesis yielded sterile, greenish-yellow fluid containing 1370 leukocytes and 240 erythrocytes per cubic millimeter. Approximately 55 per cent of the leukocytes were large mononuclear, the remainder lymphocytes and neutrophils. Cold hemagglutinins were present in high titer, 2048.

5. This patient experienced encephalomyelitis following a mild attack of atypical pneumonia. On the 18th post-inoculation day symptoms and signs of meningeal irritation appeared. Subsequently, drowsiness, transient paralysis of the bladder and rectal sphincter, paresthesias of the arms and legs and loss of abdominal and cremasteric reflexes developed. The cerebrospinal fluid was clear, sterile, and contained 17 mononuclear cells. Chemical determinations were within normal limits. The neurological findings indicated a diffuse pathological process. Recovery was complete after 2 months.

The results of this second experiment appeared to indicate that primary atypical pneumonia, as well as minor respiratory illness, was transmissible with secretions of the respiratory tract of patients with atypical pneumonia. Consideration of these cases with respect to the types of inoculum received, however, revealed unexpected findings.

There were cases of atypical pneumonia and minor respiratory illness not only in the groups receiving untreated and filtered inoculum but also in the group given supposedly non-infectious, auto-claved material. A higher percentage of illnesses was noted in those given untreated and filtered inoculum and there was a fairly uniform incubation period in these two groups of cases. However, the validity of these differences was open to question in view of the occurrence of cases in the control group. It was evident that the disease had been transmitted successfully, but the question of the filterability of the agent was not decided.

A number of possibilities were considered in explanation of these unexpected findings. Without going in to a discussion of all of the possibilities, it appeared that errors in technique arising from 1) use of the air-pump, or 2) air-borne infection at the time of inoculation were the most likely explanations. Accordingly, the experiment was repeated with major modifications as follows.

1) The inoculations were given out-of-doors and on different days and a tank of nitrogen supplanted the motor-driven power spray.

2) Partitions in the hallways were erected between groups of patients in order to prevent inadvertent air-borne cross-infection.

3) The volunteer group was enlarged to increase the possibility of demonstrating the existence of a latent agent.

4) Inocula obtained from patients with pneumonia occurring in the previous experiment were utilized in order to provide opportunity for passage of the agent.

In this third experiment there were 42 men; 12 received untreated inoculum, 12 the same material after filtration, and 18 autoclaved inoculum. There were 6 individuals who developed illnesses characteristic of primary atypical pneumonia who had been given filtered or untreated inoculum. No cases of pneumonia developed in the control group who received autoclaved inoculum.

Onset of disease in cases given the filtrate occurred on the 12th, 13th and 14th days, respectively after inoculation. Onsets occurred earlier in those receiving untreated inoculum, namely on the 7th or 8th day after inoculation. Cold hemagglutinins developed in the sera of five of the six cases of pneumonia. As noted in the previous

experiment cultures of the throat, sputa and throat washings yielded no indication of a direct etiologic relationship between any bacteria and atypical pneumonia.

There were eleven individuals who developed minor respiratory illnesses. In 10 of these patients onset of illness occurred between 5 and 15 days after the inoculation; in one individual onset was on the 19th day. This person who received autoclaved inoculum was the only volunteer who "broke" isolation having had intimate contact with another volunteer prior to the latter's illness. The clinical features of these minor illnesses were variable and resembled those noted in the previous experiment. Seven illnesses were extremely mild with minimal symptoms and signs. Four illnesses were more severe and diagnosed "suspected atypical pneumonia" because the clinical course, including the presence of rales, was characteristic of atypical pneumonia, although no roentgenographic evidence of infiltration was found.

Ten days after inoculation of filtrate this individual noted gradual onset of sore throat and hoarseness. Moderate pharyngeal injection and lymphoid hyperplasia were the only abnormal physical signs noted at this time. On the 12th day, a short febrile illness began which was accompanied by chilliness, feverishness, malaise, cough and sputum. Fine rales and rhonchi were audible over the right lower lobe. Roentgenograms showed prominent hilar markings on the right but no evidence of pneumonic infiltration. A rise in titer of cold hemagglutinins was demonstrated in the patient's serum.

The results of this experiment indicated clearly that primary atypical pneumonia was induced by bacteria-free filtrates of sputa and throat washings as well as by the same pool of material before filtration. In the third experiment, the inoculation of autoclaved material resulted in no illnesses which could be ascribed to this procedure. It appeared probable, therefore, that the cases which occurred following inoculation of autoclaved material in the prior experiment had resulted from inadvertent infection. Moreover, the experiment provided evidence against the hypothesis that the illnesses were induced nonspecifically by the stimulation of a latent agent which was present in the respiratory tract. Thus, the etiologic agent appeared to be filtrable; it was presumably viral in nature and was passed successfully in two groups of well persons.

As a result of these studies data have accumulated regarding the incubation period of experimental atypical pneumonia. Individuals receiving untreated material developed symptoms of disease approximately one week after inoculation. The onset of illness in those inoculated with filtrate occurred later, or approximately two weeks after inoculation. It appears reasonable to suppose that this discrepancy arose as a result of a decrease in dosage occasioned by the filtration process. Whether these observations reflect the chain of events which occur in the naturally-acquired infection is unknown. Factors of dosage, virulence of virus and host susceptibility and immunity have yet to be determined in the naturally-acquired infection.

These studies have furnished limited experimental data bearing on the possible relationship between primary atypical pneumonia and certain minor respiratory illnesses which affect man. The clinical similarity of some of these latter cases to atypical pneumonia was striking, particularly in those who had moderately severe illnesses and exhibited respiratory symptoms, rales and cold hemagglutinins. Roentgenographic evidence of pulmonary infiltration, however, was not found. These illnesses in many instances resembled those observed on the respiratory wards of Army hospitals. Thus, these studies provide experimental evidence in favor of the existence of a *non-pneumonic* form of atypical pneumonia as suggested by Gallagher and by Reimann and associates. It does not necessarily follow, however, that all naturally-acquired minor respiratory illnesses are caused by the virus of atypical pneumonia. The capacity of the "common cold" virus and the influenza viruses to produce minor respiratory infections is too well known to require comment. That other respiratory viruses undoubtedly exist is suggested by recent studies of the Commission on Acute Respiratory Diseases. These studies will be the subject of an address by Dr. John H. Dingle before your Societies in the near future. Suffice it to say at this point, however, that progress has been made in our understanding of the etiology of some of the respiratory diseases. Until such time as the various viruses have been isolated, characterized and properly integrated in the complex mosaic of respiratory diseases, our knowledge concerning their potentialities for disease must be considered extremely limited.

# The Atomic Bomb Experiments in the Pacific, with a Consideration of the Relationship of Atomic Energy to the Future of Medicine*

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WITH cold and scientific calculation, devoid of ceremony, the mightiest drama since the surrender of Japan was consummated in the tiny Marshall Island atoll of Bikini this summer. Two tests were made, Test Able being the atomic bomb that was detonated above the water on July 1st and Test Baker the one that was detonated under the water of the lagoon on July 25th, 1946.

As calmly precise as a laboratory experiment on possibly the grandest scale in history, the "Operation Crossroads" was planned as a series of tests, to help determine the future of navy construction, strategy and tactics.

The purpose of the tests was simple and logical. The atomic bomb is a device utilizing the phenomena of nuclear fission to produce an explosion. The explosion is unparalleled in its magnitude. A great deal of our knowledge concerning the bomb's power and characteristics has been assembled as a result of studies following the explosions at New Mexico, Hiroshima and Nagasaki, but there is a considerable amount of further information to be obtained, and it was with this idea in mind that the "Operation Crossroads" was planned. Some of the information sought was military and some was scientific.

Crossroads is an Army and Navy undertaking organized as Joint Task Force One, under the command of Vice Admiral W. H. P. Blandy, USN. The task force was composed of eight task groups, each covering a particular phase of the experiment. The task groups were further divided into 37 task units. In addition, there were two other groups closely allied but not under the task force command: the joint Chiefs of Staff evaluation board and the President's evaluation commission (1).

Crossroads was a tremendous enterprise. The job of assembling, operating and supplying the ships and men involved in the test was in itself an undertaking which compared in size and complexity with a major wartime operation (1). Approximately 42,000 men and 250 ships participated in the operation (1). In addition it was necessary to plan for the gathering and recording of the results of the tests in order that those observations might be evaluated.

Some of the commanding officers and their duties included the following (1):

(1) Admiral W. S. Parsons, USN, was Deputy Task Force Commander for Technical Direction. Under his command was a scientific and engineering staff who studied the blast from the air, the surface of the ocean and beneath the surface.

(2) Admiral T. A. Solberg, USN, was concerned with the "postmortem" of the target ships, the study of which yielded vital information for future ship construction.

(3) Dr. Ralph A. Sawyer, Technical Director of the Crossroads, was in charge of the broader field of study having to do with measurement of the phenomena attending the bomb explosions. Dr. Sawyer was in charge of nine divisions of the technical staff: (a) bomb operations, (b) blast, (c) pressure, (d) shock, (e) wave motion, (f) oceanography, (g) electro-magnetic propagation, (h) electronics, (i) radiological safety, (j) radiometry, (k) radiation, (l) remote measurements, (m) and technical photography.

(4) Dr. N. E. Bradberry, the Director of the Los Alamos Laboratory of the Manhattan Engineer District, was responsible for the bomb operation.

The civilian scientists of the technical staff from the Los Alamos Laboratory were responsible for the recording of the explosion and its accompanying phenomena, blast, pressure and shock. They were asisted in this work by the civilian and service personnel from the Navy's Bureaus of Ordnance and Ships. In order to assist them in their observations, there were Navy *drone* units

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from the carrier Shangri-La and an Army *drone* unit.

Bureau Ordnance parties were primarily concerned with pressure and shock in free air and water, independent of ship structures, and they utilized a number of different instruments *to record* those observations (1).

Bureau Ships parties were detailed to measure the structural damage to target ships, to their machinery and equipment (1). They likewise used a number of instruments to assist in recording such observations.

The Army and Navy drone aircrafts carried special instruments to the proximity of the blast in order to record and report the effect of the detonation waves on the operating characteristics of aircraft (1).

In the field of wave motion and oceanography, special studies were made (1). These included measurements of the vertical motion of target ships and buoys at a distance from the explosion. Recorders were placed on the bottom of the lagoon to measure the hydraulic pressure. Extensive photographic records were made of the surface waves and the motion of the target ships under wave action. Seismographs were set up on the Islands of the atoll to record the propagation of the shock waves through the earth yielding information, thereby, on the geology of the atoll. The oceanographic studies also included before and after surveys of the geology, flora, fauna, and fisheries.

(5) Dr. E. W. Thatcher was in charge of the studies of the effect of the atomic bomb explosion on the propagations of electro-magnetic waves (1). These studies were carried out by Captain C. L. Engelman of the Navy's Bureau of Ships, and Colonel D. F. Henry of the Army Air Force. Among other things, they were concerned with the influence of the intense local ionization, resulting from the explosion, on radio transmissions. They observed the radar reflective properties of the bomb cloud and the intensity of the atmospheric electrical disturbances.

(6) Colonel Stafford Warren of the Manhattan Engineer District was in charge of the protection of personnel from radiological hazards from the blast. Under his direction there were a number of physicists, chemists, engineers, instrument men and some civilian personnel. Colonel Warren's influence was felt everywhere. There was scarcely a single operation in which he was not directly concerned because the safety of the personnel was paramount.

(7) Dr. Edward Hulbert of the Naval Research Laboratory coordinated the studies concerned with radiometry (1). These studies included the measurement of light in the visible spectrum and adjacent wave bands, such as infra-red and ultra-violet. The measurement of the various radiations given off from the bomb were under the direction of Dr. M. Holloway of the Los Alamos Laboratories.

The photography of the bomb was under the direction of Captain R. S. Quackenbush, Jr., USN (1). Never was there a single operation in which there was such an array of cameras focused as there were in the two tests carried out this summer. Ground and aerial photographs recorded all phases of the operation. Four B-29's tracked and photographed the atomic cloud to determine its persistency and radiological activity. Four more F-13's and B-29's adapted as photoaircrafts covered the Bikini atoll during all phases of the blast to obtain material for technical analysis, reaction of the target ships, and an analysis of the damage done to the ships and the target area. Two special AAF C-54's photographed the detonations for analysis of the shock wave, and there were four Navy F-6F aircrafts which recorded the target area in the last few moments before the blast, and two sections of Navy torpedo bombers circled the bomb cloud after the blast photographing it from every angle. From the ground, radio-control cameras installed in 75 ft. steel towers around the atoll recorded the event at close hand. Thus, a complete record was amassed by the various task units under the direction of Dr. Sawyer.

The target ships included some of our proud fighting ships with valiant war records. Many of the various types of ships were included in the target array such as destroyers, submarines, attack transports, landing ship tanks, landing craft infantry, LCT's, LCM's, floating dry docks, barges, cruisers, aircraft carriers and battleships. These target vessels were strategically concentrated in the lagoon in the immediate vicinity of the "bull's eye" in order to test the effect of the bomb on the various types of vessels. The detailed knowledge of the destructive power of the bomb should provide the Navy with information concerning any change in ship designs, tactical formations at sea and the anchoring distances in ports. Other information obtained was the effect of the atomic

bomb against aircraft, both airborne and grounded, and the effect on a wide variety of weapons and equipments.

An important consideration in the test was the effect of the irradiation on living beings. This was necessary in order to provide much needed information on protection, early diagnosis and treatment of personnel, who may in the future be exposed to atomic bomb radiations either in war or peace.

It is recalled that in the New Mexico experiment of the atom bomb, temperatures of fantastic proportions crumpled a steel tower. On the basis of that experiment it was predicted that the terrific blast of heat would undoubtedly cause considerable damage in the immediate vicinity of the detonation. Those of you who have seen movies of the Able test are familiar with the damage that was created as a result of direct heat radiation and the secondary damage due to explosions of ammunition, gasoline and other inflammables.

In the two Japanese explosions direct heat radiation was responsible for many casualties. The much publicized radio-active after-effects were also the cause of many deaths and injuries. From the Bikini test, knowledge was obtained concerning the relationship between the distance from the blast and the degree of injury and the efficacy of protection offered by steel plates. Information was also obtained on the possibility of radioactive material entering protected spaces through ventilation ducts.

Many of you will recall the predictions of water disturbances to be caused by the underwater detonation of the bomb. These predictions varied from conservative 70 ft. waves, in the immediate vicinity of the explosion, to semihysterical alarms of the uninformed, who painted horrifying visions of bomb-born tidal waves engulfing cities on distant shore lines. It was foreseen that ships near the explosion center would be subjected to the terrific stresses but it was not until after the Bikini test blast that the real information was obtained.

The island of Bikini was transformed into a robot laboratory in which automatic cameras and recording devices of various types recorded scientific data concerned with the explosion. The work on Bikini Island was performed by the 53rd Seabee Battalion, veterans of Guadalcanal, Vella Lavella, Bougainville, and Guam (1).

The lagoon, which is about 10 miles wide and 20 miles long, is about the size of the San Francisco Bay. It was divided into sectors and the target ships were placed within these sectors. On Able minus one, the ships of the fleet, other than the target vessels, left the lagoon and took up prescribed stations. These stations were approximately 20 miles away from the target area. Even at that distance we were warned that it was not safe to look at the flash of the exploding bomb. On Able day the weather was perfect. There was good visibility and a constant air movement. Therefore, the test proceeded according to plans. Aircraft of the task force were the first to enter the lagoon after the blast because it was expected that the air would become free of radioactive particles more rapidly than the water. In a relatively short time, the fleet was ordered to approach the lagoon carefully testing the water as it advanced. After it had been found safe to re-enter the lagoon, the various patrols began to monitor the sectors assigned to them, and in due time an outline of the extent of the radioactivity was recorded.

The success of tests from an information standpoint depended to a considerable extent upon the rapidity with which the monitoring of the lagoon and the target ships could be obtained, because it was only after such information was obtained that the salvage teams were able to swing into action to control secondary fires and internal explosions. Likewise, it was essential that boarding parties return to the ships as soon as it was safe, in order to collect the animals from the ships, remove the scientific instruments, and to observe the effect of the bomb on the ships and its equipment. This was a tremendous undertaking and one of the most important of the entire operation. Three weeks were alloted to the collection of this data.

For the Baker test, the same general plan was carried out except that this time it was unnecessary for the fleet to be as far away as in the Able test, and it was possible to look at the blast without injury to the eyes. Following the detonation of the bomb we again entered the lagoon but we did so more slowly than in the first test. The Baker test was a much more serious undertaking than I had conceived before the detonation of the bomb. The radioactivity was more intense, and it was necessary to exert a greater degree of vigilance in order to protect the personnel of the fleet.

The operation is still being carried on. There is still a tremendous amount of work to be done. Some of the ships are still radioactive and probably will be for some time to come.

The first two tests at the Crossroads, to my

mind, represented the greatest pageant of all times. The fantastic nature of the physical forces brought into play, the mighty effects of radiation and the tremendous array of ships and men concerned with this test were most impressive.

I have not seen any official figures on the results of the two bombs on the animals but in *Time*, September 16th, page 100, it is stated that the Navy told about the animals' *ordeal*. "At test Able, which was the air-burst, there were 3,030 white rats, 176 goats and 146 pigs on 22 target vessels. Some were near the blast center, some far off, some were sheltered, some exposed. About 10 per cent died at once of the air blast; 10 per cent more had died chiefly from radiation sickness by late August. The same number, presumably injured, were killed for examination.

"At test Baker, the score was higher. Two-hundred white rats and twenty pigs were confined into sick bays of four ships near the bomb. All were well sheltered and none of these ships were sunk but 77 rats were dead soon after the blast. Forty-nine died later of lingering radiation sickness. Of the twenty pigs, no pig came home. Six were found dead when their shelters were entered four days after the explosion. All the rest died in two weeks."

Captain Shields Warren has recently reported on the pathologic effects of an instantaneous dose of radiation, as a result of his studies at Hiroshima and Nagasaki (3). He describes a vivid picture of what can be expected from atomic bomb explosions, similar to those observed at Bikini. The pathological effects were divided into two groups: First, the effects of heat producing primary thermal injury of the flash burn type, and secondary thermal injury due to induced fires. Second, the effects of radiation. At the time of Captain Warren's study, 80,000 people had died in Hiroshima and 45,000 at Nagasaki.

The characteristic clinical course of those persons primarily suffering from radiation injury as a result of the atomic bomb explosions may be divided into two stages. The immediate effects were manifested as weakness, malaise, fever and often death within forty-eight hours. The delayed effects manifested themselves in a variety of ways.

The effect on the blood could be readily followed by the clinical manifestations as well as the laboratory observations. The patients were divided into three groups. The first group was those occurring early with marked leukopenia, in which infection and particularly Ludwig's angina was the outstanding manifestation. In a great many of these, death occurred in the first three weeks. Following that, the *second* group which lived from three to five weeks (after the bombing) had a number of hemorrhagic deaths associated with thrombocytopenia and marked effect on the bone marrow. There were extensive ecchymosis to purpuric patches and small petechia. Mucosal hemorrhages occurred everywhere. In the *third* group, there was serious bone marrow damage with anemia. At times the marrow was so depleted that little but reticulo-endothelial cells appeared.

The gonadal effect was much more prominent in the male than in the female. Atrophy of the germinal epithelium of the testis was marked. There was suppression of menstruation found in some of the high school girls. A recent survey by Colonel James Cooney of the Walter Reed Hospital showed that sterility has become more of a problem than was anticipated. Many flesh burns are still unhealed and keloid formation is tremendous. There is still a large number with bone marrow deficiencies. Observations will have to be carried on for many years to learn the total effect of instantaneous exposure such as occurs following detonation of bombs similar to those in Nagasaki and Bikini.

The discussion thus far has been on the use of atomic energy as an instrument of war. What are some of the prospective medical uses of atomic energy? Many papers have been written on this subject. One of the best is written by Dr. W. Edward Chamberlain and was presented in May as one of the George Westinghouse memorial lectures. Plans are now under way by the Manhattan Engineer District to release a great many radioactive isotopes for medical investigation and treatment. The immediate application of such isotopes to medical problems is so certain that it can be predicted with considerable assurance that it is by advances in therapeutics, in medical science, in biology, and in chemistry that the greatest peace time reward will be associated directly with the next ten years of the "atomic age."

It is stated that the chain-reacting Uranium Piles, such as those located at Hanford, are sources of neutrons and other radiations equivalent to more than a million cyclotrons (2). These neutrons which were used to produce new elements plutonium may also be used to produce in quantity long-lived radio-active carbon and hydrogen (2).

These elements will make possible, for the medical research worker, the labeling with radioactivity of those organic compounds that play essential roles in the animal and human body, both in health and disease. Almost every organic chemical entity of possible concern in biology or medicine contains one or both of these elements in key structural positions (2) This means that by the proper chemical or, if necessary, biological synthesis it will be possible to obtain most organic compounds of medical or biological interests with radioactive labels.

For some years radio-phosphorus, iron, sodium, iodine, strontium, sulfur, and potassium have been among those materials used in medical investigations and treatment. Most of us are familiar with the use of radioactive phosphorus in the treatment of leukemia and polycythemia. Strontium has been used experimentally in the treatment of bone tumors. Iodine has been employed in the investigation of thyroid metabolism, in the treatment of hyperthyroidism, and carcinoma of the thyroid. According to Bale none of these radioactive isotopes are comparable in their usefulness to that of radio-carbon or hydrogen in the fields of medical research, since each one is usually absent or loosely attached to the key structural group of most organic compounds (2).

Radioactive carbon will have important applications in cancer research, in pharmacology, in biology, in medical therapeutics, and in medicine in general. The study of the metabolism of malignant tumors is one of our foremost problems. There still remains considerable basic research to be done on aging and the degenerative diseases. Bale in discussing this general subject states that we still need to know fundamental things such as how much of the cell is formed permanently during its early development, and what portion is renewed from metabolites supplied by the blood stream. We need to know what factors are important in cell and tissue degeneration and whether we can influence its speed and magnitude in any way. How do the different types of tissue cells in an aging animal differ in their metabolism from cells of the young and early adult animal?

Comprehensive metabolic studies using tracer technique should provide a basic foundation of knowledge from which it may be possible to obtain an insight leading to an increasing human adult span of productivity and pleasant existence. Radioactive isotopes are the new tools that are of such fundamental importance and they will soon see nationwide and world-wide use.

In the September 17th World Report there is a special editorial on the "atomic bomb" as a military weapon. Some of the points brought out in this editorial are abstracted as follows:

The one basic and all-important fact concerning the atomic bomb is that it transcends all previous efforts of mankind in the long history of warfare.

The bomb already has altered and will continue to affect the political and military pattern of the world. The question of control of the bomb is now the subject of negotiation and debate.

The atomic bomb has increased vastly the possibility of devastating attack without declaration of war and of pre-war sabotage on a catastrophic scale.

The destructive capacity of the bomb on land is well known as a result of the explosion over Hiroshima and Nagasaki. Exploded in the air at a selected height, it will destroy all normal land structures and most life within a radius of a mile and a half. There will be an additional area of less damage and an extensive delayed effect largely fatal to life, due to radioactivity.

The first Bikini test determined the effect of an air explosion over a closely concentrated group of vessels at anchor. The results indicated that such a bomb would damage fatally even large war ships within an area of half a mile and inflict damage to exposed structures on a diminishing scale up to a mile. Exposed personnel in this area would be killed or incapacitated.

The second Bikini test determined the effect of a shallow submerged bomb under a closely concentrated group of vessels at anchor. This underwater explosion indicated that such a bomb would sink or seriously damage even large Naval vessels at a distance of 500 yards and damage to less degree other vessels up to 1,000 yards. It resulted in extensive and persistent radioactive effects on water and ships.

The atomic bomb as a military weapon will have far-reaching effects on the technique of warfare.

It will increase the totality, the complexity, the horror and the cost of war.

It will establish science as an additional defense force of every great nation.

Mr. Bernard M. Baruch has presented the American proposal for International Control to the members of the United Nations Atomic Commission. His report met with acclaim from most

of the nations except Russia and her satellites. In fact, Mr. Andrej Gromyko has presented the Russian proposal for International Control. Both of these reports should be studied by all of us.

The problem of how to avert atomic disaster is still very new. Only tentative solutions can be brought forth at this time. One thing is certain, we cannot expect to hold up the peace time uses of atomic energy even for security.

Fortunately we do have the embryonic organization, the United Nations Council. It is possible for it to grow. There is no other way known at present which can establish effective safeguards against war and mass destruction.

The United States has a great opportunity to assume an aggressive leadership in the formation of a world order of universal law, because of its preeminence in military power.

What can you and I do to assist in the movement of peace? This problem is ours. As you know, atomic energy and atomic bombs are marked "made in the United States." Soon they will be made elsewhere.

We can make it our business to keep informed about atomic energy and in turn keep our representatives conscious of their obligations to strive for everlasting peace. We can join the movement of the atomic scientists. We can make contributions to help defray the expenses of the propaganda these scientists are fostering. The United States, thru the United Nations, must become as aggressive in peace as she was in war. Before the world, we must be united in our aims. Even then the progress will be slow and it may be necessary for us to sacrifice more for peace than for war. Above all, we must not become discouraged.

If we can develop a plan for and have peace, *all nations can have atomic energy and much more.*

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# Benjamin Rush from the Perspective of the Twentieth Century*

*By* RICHARD HARRISON SHRYOCK, PH.D.

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IT has recently been observed that "One often hears and sees Rush's name mentioned, but in a few tiresomely repeated connections; as a man and as a writer he is little known".[1] This is doubtless true so far as the general public is concerned: in contrast to his friends John Adams and Jefferson, Rush has been largely forgotten even by the well-informed. This may be explained, in some measure, by the political emphasis which characterized American historical writing until recent decades. Despite some interesting adventures in public office, Rush was never a major political figure; hence he was neglected by writers primarily interested in constitutions, parties, and affairs of state.

During the present century, scholars concerned with special phases of American history, notably with educational and literary developments,[2] began to give Rush serious attention; and as the interests of general historians broadened, they noted his contributions to social reform.[3] In 1934 Nathan Goodman brought out the first full-length biography, which presented the whole man "vigorous in mind and body, and heroic in stature."[4] During the last few years, renewed interest has been manifested by literary historians. Notable is the current work of L. H. Butterfield, who, in cooperation with the American Philosophical Society, is preparing an edition of selected correspondence and also a Union Catalogue which will provide the first systematic guide to Rush's voluminous writings.[5] It seems likely, therefore, that Rush will receive wider attention in the future from scholars at large.

We are not primarily concerned here, however, with the rediscovery of the man by general and literary historians. In contrast with such writers, physicians and medical historians never forgot the Philadelphia leader, and comments on him have continued to appear ever since his death in 1813. An interesting essay could be prepared on the history of this literature *about* Rush; and this might throw light on changing medical perspectives over the years, as well as on the physician himself. One can only suggest the features that such an essay might assume. It would relate, first, to the often-controversial contemporary writings; next to the eulogies of 1813; then to more basic criticisms appearing after 1820, which swelled to a chorus of condemnation during the '40's and '50's. Unfavorable mid-century reactions reflected the growing influence of French medicine in America, which repudiated nearly everything for which Rush had stood. These reactions were typical of most professional appraisals until our own time, save as these were tempered, in the case of Philadelphia critics, by a natural pride in a great local citizen.

A more balanced view became possible during the present century, as medicine returned in some degree to eighteenth century concepts. The attention recently accorded his work in psychiatry affords an obvious illustration of this renaissance of appreciation.[6] In certain respects, Rush's views no longer seem so strange to present medical thinkers as they did to those of 1850.

Yet even during recent decades one still encounters those extremes of opinion, those sharp contrasts of censure and praise, which characterized earlier writings. During the first half of the last

* Benjamin Musser Lecture III, The College of Physicians of Philadelphia, read at a Special Meeting of the College, November 6, 1946, commemorating the 200th anniversary of the birth of Benjamin Rush, one of the founders of the College.

[1] Lyman H. Butterfield, *Year Book* of the Amer. Phil. Soc., 1945, p. 191.

[2] As in Ellis P. Oberholtzer, *The Literary History of Philadelphia* (Phila., 1906); and the careful study by Harry G. Good, *Benjamin Rush and His Services to American Education* (Berne, 1918).

[3] *E.g.*, John Krout, *The Origins of Prohibition* (N. Y., 1925).

[4] Univ. of Penna. Press, Preface.

[5] Note 1, above, 190ff.

[6] See, e.g., Clifford B. Farr, "Benjamin Rush and American Psychiatry," *Amer. Jour. Psychiatry*, Centennial issue, 1944; R. H. Shryock, "The Psychiatry of Benjamin Rush," *ibid.*, vol. 101 (Jan. 1945).

century, there had been such divergent opinions as those of Dr. Elisha Bartlett and (somewhat earlier) of Dr. Lettsom of London. The former made the acid observation that there was more "utter nonsense and unqualified absurdity" in Rush's works than in the whole vast compass of medical literature;[7] while Lettsom went to the other extreme in claiming that the Philadelphian combined judgment and sagacity "in almost unprecedented degree."[8] Similarly extreme contrasts of opinion appeared as late as the 1920's and '30's. Dr. Victor Robinson, for example, observed in 1929 that "the career of Rush proves that . . . a physician with a facile pen may leave behind him several volumes entitled 'Medical Inquiries and Observations'—and not one page of scientific value. . . . There are few medical writers, and certainly none of celebrity, whose works are less worthy of perusal today than those of Rush."[9] Yet only a few years later Dr. Goodman claimed that Rush was extraordinarily successful in his treatments, and that he anticipated modern medicine in many ways.[10]

Such conflicting opinions, persisting over so long a period, suggest that we are dealing here not only with changing scientific perspectives but also with an unusually positive personality. This personality was so sincere and devoted, and yet so self-assured and aggressive withal, that it has continued to make friends and enemies throughout these many years. Hence there remains room for honest differences of opinion about Rush the man.

It should be possible, on the other hand, to approach agreement concerning the doctor's theory and practice—as measured by the science of his day—and to evaluate his place in American medical history. Subjective reactions to his personality have no place in such an analysis, which relates to what may be well viewed as the most important aspect of Rush's career. Certainly the "American Sydenham" was first and foremost a physician. Important as were his political, social, and literary contributions, he was primarily devoted to medicine. In this field alone was he *the* outstanding national leader. In practice, he seems to have viewed his political and social activities as those which any public-spirited physician should undertake; that is, these activities were incidental to the scientific career. Here there was an interesting contrast with his friend Franklin. For the latter, although declaring the primacy of scientific interests, seems actually to have subordinated them to public affairs.

For the sake of simplicity, the analysis of Rush's medical work may be limited to the well-rounded theory and practice of his later years—which means primarily the period following the great yellow fever epidemic of 1793. An analysis of his earlier views and of how and why these changed would not be without interest; but it was the final "system" which became the subject of controversy and on which Rush staked his permanent reputation.

Most basic to an understanding of this system was his theory of pathology, or of what he termed the "proximate cause" of disease. He began by claiming that all fevers resulted from (1) a predisposing debility; (2) a stimulus which was the immediate, inciting cause, operating upon a debilitated body to produce (3) a convulsive excitement or "excessive action" in the walls of the blood vessels. This last condition, which related more to pathologic physiology than to pathologic anatomy, was viewed as the essence of the fevers. Subsequently, he declared this "convulsive action" to be the underlying feature of all apparently distinct forms of illness. "I have formerly said," he declared to his students in 1796, "that there was but one fever in the world. Be not startled, gentlemen; follow me and I will say there is but one disease in the world. The proximate cause is irregular convulsive or wrong action in the system affected. This . . . is a concise view of my theory of diseases. . . . I call upon you, gentlemen, at this early period either to approve or disapprove of it now."[11]

Stated as bluntly as this, the theory now sounds absurdly over-simple. Further analysis, however, shows that Rush was dealing here with basic problems which cannot be ignored in any concept of disease. Predisposing debility was analogous to the modern idea of "lowered resistance." It might be caused by fatigue, intemperance, faulty diet, emotional disturbances, and various other processes.

"Stimulus" (the immediate, inciting cause) was conceived broadly enough to include anything which would be listed today as an external etiologic

[7] *The Philosophy of Medical Science* (Phila., 1844), 225.

[8] *Recollections of Dr. Rush* (Lon., 1815), 12ff.

[9] *Medical Life*, vol. 36 (Sept., 1929), 445, 447.

[10] *Benjamin Rush*, 235, 254, etc. References to various opinions of Rush are appended to this work, and also to the author's article on Rush in the *Dict. of Amer. Biog.* Dr. Butterfield's finding lists will doubtless add more.

[11] Lectures on the Practice of Physic, I, No. 31; II, No. 1 (*MSS.*, University of Pennsylvania Library).

factor. Rush did not distinguish clearly between circumstances producing debility and those acting as direct stimuli; thus he listed emotions—psychosomatic relations—under both headings. But note that he viewed the genesis of each illness as involving two circumstances—the impact of an outside agent and the reaction of the body itself. This view, later lost to sight in the preoccupation with bacteria as the sole "cause" of certain diseases, is analogous to the modern idea that the "cause" of an infection is really a complex relationship between body cells and infectious agents.[12]

Where Rush departed from views already held by some in his own time, and more universally accepted thereafter, was in his concept of the stimulus factor. He insisted that this was entirely nonspecific in nature. All stimuli, no matter what their character, were said to produce the same effect; that is, the pathologic process of excessive action in the vascular system. The body was capable of only this one primary form of pathologic reaction, much as the optic nerve and visual center react to any stimulus whatever in terms of sight. To be sure, the pathologic process expressed itself in different symptoms having different names —in a fever, a pleurisy, a dropsy, and so on. But any one of these clinical pictures could be produced by any sort of stimulus if the latter were strong enough. Rush knew that certain etiologic factors (for example, smallpox virus) seemed to be specific, but he expressly denied this. "My view," he declared, "establishes the sameness of a pleurisy, whether it be excited by heat succeeding cold, or by the contagions of the smallpox and measles, or by the miasmata of the yellow fever."[13]

This might be interpreted to mean simply that different causative factors may produce similar symptoms—a truism in itself—were it not that Rush denied specificity in pathology as well as in etiology. All external factors were able to produce the same symptoms because all of them led to the same underlying pathologic process. This process, in turn, could produce the variety of clinical pictures noted; though it is not clear in Rush's writings why it sometimes revealed itself in a dropsy and at other times in a fever. Whence came this basic doctrine of the underlying unity of disease?

Any attempt at explaining the origin of Rush's doctrine must take into consideration many phases of his thought as well as the chief medical problems of his day. There was no one, determining circumstance, but rather a convergence of influences—scientific, professional, and social—which led the physician toward this extreme position.

It is to be remembered, first, that monistic pathologic theories had been inherited from classical times. Stated very simply, these had ascribed disease processes either to the condition of the body fluids (humoralism) or to an alternating tension and laxness in the solid parts (solidism). The latter hypothesis was usually explained in terms of tension and laxity in the nervous or vascular systems, since these reached nearly all parts of the body, and any irregularities in them would therefore seem to explain the wide dispersal of symptoms —the fact that the ill man often seemed "sick all over." (It later proved difficult for the localized pathology of 1830 to explain this phenomenon.) In a general way, Rush may be identified with the persistence of this *strictum et laxum* tradition. Much interest had been displayed in it at Edinburgh where Rush was trained, and the immediate background of the latter's theory seems to have been an elaboration of this type of "system" by his fellow-student, John Brown.

Indeed, Rush was viewed in Europe as a sort of Brunonian, though he took pains to point out differences between this school and his own. Among other distinctions, Brown viewed "debility" as a lack of tone in body systems, and held that this was one of two main types of pathology, the other being excessive tone or action. But Rush insisted, as noted, that debility was not in itself disease but only a predisposition; and that the only truly pathologic condition was tension.[14] He thus reduced Brown's dualism of laxity and tension to the strictly monistic doctrine that tension alone was the substratum—the *ding an sich*—of all illness.

Why, however, after the brilliant advent of modern methods in medicine during the seventeenth century, was there this seeming reversion to classic speculations in pathology as late as 1800? This resulted, in part, from the very advances made in biological science during the interval between Harvey and Rush. So many new facts had been discovered that confusion was threatened, unless

[12] Wiley D. Forbus, *Reaction to Injury* (Baltimore, 1943), 45ff.

[13] Quoted by Goodman, *Benjamin Rush*, 232.

[14] Owsei Temkin, Comments on the German translation of Rush's account of Yellow Fever (*MS.*, 1946, to appear in the *Festschrift* in honor of Dr. Victor Robinson).

these could be interrelated by some all-embracing theory. At the very time that Rush was formulating his ideas, his teacher Cullen at Edinburgh declared: "For, when many new facts have been acquired, it becomes requisite that these should be incorporated into a system, whereby . . . the whole may be rendered more complete, consistent, and useful."[15] The Philadelphian took his master seriously.

No better illustration of the confused state of medical science could be had than the state of nosography—of disease identification and classification—in Rush's day. Through the centuries a number of striking clinical pictures had been recognized, such as "consumption" and certain skin diseases; but the first conscious, systematic attempt to identify distinct forms of illness came with the seventeenth century. Thereafter, the authority of Sydenham gave this search considerable impetus. Logically, it represented the first truly rational approach to medicine, for how could there be an intelligent study of causes and cures of diseases until the diseases themselves had first been found?

Unfortunately, the only criterion which first appeared for disease identification was that of symptoms. This served well enough when these signs were obvious to all, as in the case of the "great pox" or of the "small pox." But the symptomatic classification of various fevers as "remittents," "intermittents," "continuing," "putrid," etc., was not so helpful. And as enthusiasm grew for identifying all possible symptom combinations as separate entities, long lists were prepared in nosography texts which amounted to only so many names. Rush rightly felt that these texts were most confusing, and desired some simpler scheme which would really aid the practitioner. He therefore swerved to the other extreme—from the listing of innumerable, supposed disease entities to the flat assertion that there was only one.[16]

There was, of course, a middle way between these extremes, one that eventually led out of nosographical confusion and thereby made modern medicine possible. This was the search for a localized, structural pathology. Once local lesions were charted and then correlated with ante-mortum symptoms, a basis for disease identification was secured which was far superior to symptom lists on the one hand or assumptions about disease unity on the other. Had the merely symptomatic nosography persisted, no one would ever have found either causes or cures for the long lists of names. Worse still, had the theories of Brown and Rush survived, there would never have been even a search for causes and cures, since there was nothing more to learn. Rush knew the one "proximate cause" of all disease and—as will be noted shortly—had the one means that would cure it. Accepting his premises, there was no need for further research. But the study of lesions by pathologists, and the correlation of these with clinical evidence, opened up the whole line of pathologic advance that led in turn to the development of medical bacteriology and immunology during the nineteenth century.

This more promising approach was getting under way in Rush's time. Morgagni had clearly indicated its possibilities about 1760, and shortly thereafter Dr. Thomas Bond actually explained them in a lecture at the Pennsylvania Hospital (1766).[17] Bichat and the French school were beginning intensive work in pathologic anatomy during Rush's later years. Yet the latter apparently was quite indifferent to all this promising research—rarely if ever does one find any reference to it in his writings. Originally interested in physiologic experimentation, in which his students did pioneer work in this country, Rush seems gradually to have become all-absorbed in practice. His later indifference to both physiologic and anatomic studies cannot for a moment be ascribed to laziness or inertia; he was a most intense worker, but one who by 1790 was giving nearly all his time to the bed-side and to the library.

I recall no specific statement by Rush which questions the laboratory approach, but one senses that he had little enthusiasm for it in his later years. He expressed the humanitarian zeal of the Enlightenment, and his one great purpose was to help his patients. This could not be done by turning aside to pathologic studies of no immediate value to therapy. He certainly would have repu-

[15] *First Lines of the Practice of Physick*, I (Edinburgh, 1796), 34.

[16] See Temkin's quotation (*op. cit.*) on Rush's opinion of Cullen and Brown in this connection, taken from the former's *Sixteen Introductory Lectures* (Phila., 1811), 11f.

[17] *MS.* lecture, College of Physicians of Phila. Library; printed in T. G. Morton and F. Woodbury, *The History of the Pennsylvania Hospital* (Phila., 1879), 462ff.

diated the medical nihilism that ensued after 1830. Conversely, the discovery of a "system" that promised cures for all conditions must have thrilled a man who—in the tradition of the Revolution in which he had participated—hoped to benefit all mankind.

Although Rush seems to have inherited his major thesis from classical traditions, he was not necessarily aware of indebtedness to earlier theorists. He observed that the first attempts to identify disease entities on a symptomatic basis had gone astray, and therefore cast about for some means to ending the confusion. Failing to see that the symptomatic criterion could be made really useful if correlated with pathologic anatomy, he adopted the ancient idea of disease unity,—perhaps without even considering at the moment that this *was* an ancient notion. He never supported it by appeals to authorities in a scholastic manner, but seems rather to have been impressed with the revolutionary character of his own ideas. Like other eighteenth century theorists, indeed, he would have repudiated scholasticism; for the writings of empirical philosophers and the Baconian emphasis upon inductive reasoning had long since placed a premium on direct, independent investigations of Nature.

This fact, that the most speculative medical thinkers of the eighteenth century rendered at least lip service to inductive reasoning, raises an interesting question about Rush's own thought. Did he base his theory on something more than tradition—which doubtless influenced him even if he was unaware of it—and on something more than the pragmatic realization that it was useful in clarifying nosographic complexities? In a word, did he cite any actual evidence from which to induce his theory in the first place?

Here, it must be admitted, the writings are rather fragmentary and unsatisfactory. Rush usually just stated his premises and reasoned from them, using such dogmatic phrases as "my view establishes," and so on. Often he seemed to accept analogies as evidence, and was quite clever in employing ones that were apt and appealing in his day. Thus he suggests that the physician who thinks different clinical pictures are really different diseases, is as ignorant as a savage who supposes that water, dew, and frost are distinct substances. Or, again, he compares the theory of disease unity with noble monotheism in religion, while a belief in distinct diseases is equated with a superstitious belief in polytheism. Goodman declares that this was a very modern line of reasoning.[18]

Yet, imbedded in some of Rush's lectures, are hints of an empirical starting point. As might be expected, he took off on his speculative flights from a very circumscribed field of bed-side observations. He had made the common observation that a flushed skin is associated with fevers. This was believed to indicate a distension of the capillaries. Since such "convulsive action" in the walls of these vessels was observed in *all* fevers, Rush concluded that it must be the essential pathology of these conditions.[19] Conversely, phenomena associated with some fevers but not with others—such as various symptoms or lesions—could not be essential to fevers as such. The underlying fallacy here was the initial assumption that "fever" was a sort of entity, but this was commonly held at that time. Once this was assumed, the reasoning was logical enough though just the reverse of that now employed. Rush would have held that the intestinal lesions, now viewed as the chief feature of typhoid fever, were mere after-effects of capillary or arterial distension; while we view as a secondary phenomenon the very capillary distension which he considered the essence of the disease. The doctor had the cart before the horse here; but in any case, he had them linked neatly together.

In attempting to explain the origin of Rush's "system," mention has now been made of the traditions behind it, of its pragmatic appeal in a time of confusion, and of the limited degree to which it was based upon actual clinical evidence. These explanations would be incomplete without additional reference to certain qualities of mind that lent themselves to the elaboration of ingenious hypotheses. The doctor had a keen interest in abstract and speculative questions, and was most at home in quasi-philosophical discussions. These qualities, combined with personal kindness, gave him an almost unique popularity with students; so that he probably contributed more than any other one man to making Philadelphia the chief national center of medical training.

Rush's imagination was stimulated by wide reading, and this suggested all sorts of plausible hypotheses—many of which were sound enough when applied to the social and historical problems of that epoch. Historians, who still fall back on

[18] *Benjamin Rush*, 235

[19] Richard H. Shryock, *Development of Modern Medicine* (Phila., 1936), 28, 29.

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their imagination at times, may appreciate these qualities more highly than do natural scientists. To put it more accurately, the historian is still likely to depend on his imagination in situations not admitting of final verification. He presents what seems the most convincing hypothesis; and unless quite careful, he soon writes as though the thesis were actually confirmed by the incomplete evidence available. Rush's thought operated on much this same level; that is, he began with some very limited evidence and on this basis formulated an hypothesis that was logical enough within its own structure. Then, since the thesis seemed plausible and promised cures, he accepted it enthusiastically and interpreted his clinical experience as verifying it.

All the steps in this chain of thought are sound enough until we come to the last—the failure to seek adequate verification. The treatment which Rush advocated was literally a cure-all—was good for what ailed you, since by definition the same thing ailed everyone. The procedures—which were largely bleeding and purging—will be discussed by Dr. Pepper. They followed logically from Rush's premises; for if disease consisted of vascular tension, then it could be cured by relieving that tension through bleeding. Anyone could see that, if the patient were bled copiously enough, he would relax—sooner or later! But such a superficial observation was far from providing a real verification of the soundness of the theory employed.

One should therefore pause to examine this weakest point in Rush's line of thought. How valid was his claim, for example, that he could almost always cure yellow fever by bleeding—provided the cases were not too far advanced—and that this proved the soundness of his underlying theory? In answer, it must be noted that (1) Rush's own clinical data were fragmentary—he kept no real statistics; (2) even if he had done so, the figures would have been based only on his own claims of cures. The idea of using "controls" to check a method of treatment does not seem to have occurred to him; and under these circumstances, his claims were suspect in terms of the *post hoc, ergo propter hoc* fallacy; (3) even if the physician *had* kept careful records, and checked his own treatments by the use of "controls," the limited experience of one observer was quite inadequate for the final demonstration of a sweeping hypothesis.

It is easy to show in this fashion that Rush's procedures did not measure up to present canons of scientific method, or to those which Bichat would have demanded in that day. Yet even here, one can feel some sympathy for the former's difficulties. The Philadelphian was by no means visionary in seeking clues in pathologic physiology rather than in pathologic anatomy; yet it happened that the first field offered more difficulty than the second in the way of verification. Bichat could verify his thesis that lesions were common to certain types of tissues with relative ease; whereas—given the state of physiology at the time—there was just no way for Rush to test whether a tension in capillaries caused what he viewed as mere after-effect in the form of organic lesions.

Hence he was under great temptation to seek confirmation by the only apparent means—the appeal to clinical experience. It is only fair to recall that innumerable physicians had reported, through the centuries, that bleeding did give excellent results in all manner of conditions. Doubtless Rush felt that the evidence in favor of his treatments—and therefore of his theory—was cumulative even if incomplete.

It is also to be recalled that he was no more careless in handling clinical data than were the great majority of medical men in his day. Perhaps a few individual physicians had suggested the keeping of accurate records, and had been prevented from doing this both by lack of time and lack of enough data to make it worth while. Large hospital services, bringing hundreds of similar cases under the view of a single clinician, were still pretty much in the future. Statistics and the calculus of probabilities were young sciences in Rush's day, moreover, and it was not until three years before his death that the mathematician Laplace called attention to the value of these disciplines for medical studies.[20]

Strangely enough, the first attempt to apply statistics in therapy which I have encountered is that of William Cobbett—an attempt made in the course of the pamphleteer's famous controversy with Rush. Cobbett had no real clinical statistics; but he went to the local bills of mortality to prove mathematically that the doctor was killing yellow fever patients rather than curing them.[21] In relation to the history of scientific method, this episode deserves more attention than it has received. While Rush was then in no mood to accept any

[20] *Théorie Analytique des Probabilités*, 3 ed., (Paris, 1920), 420ff.

[21] *The Rush Light* (N. Y., Feb. 28, 1800), 49.

suggestion coming from Cobbett, it is also true that physicians in general ignored this early appeal to quantitative procedures.

Within a decade after Rush's death, the French school had firmly established approaches to medicine which were the antithesis of his own. Research was concentrated on the correlation of structural lesions with associated clinical data, in the effort to identify specific disease entities. This brought with it a demand for all the more accurate methods of observation—instruments, statistics—which Rush and most of his contemporaries had ignored. As a logical corollary, the whole theory of the unity of disease was repudiated.

This theory, to be sure, has been revived from time to time down to our own day. The thrill of finding the *one* pathologic condition, with its promise of one cure, continued to appeal to certain theorists and to many laymen. No doubt Hahnemann and the early homeopaths; "Doctor" Still and the osteopaths, and Mrs. Eddy and the Christian Scientists, all felt the same exhaltation in proclaiming one cause and one cure as Rush once had in announcing his revolutionary "system." But the latter worked in a day when the weaknesses of this approach were not yet clear; whereas the others proclaimed their views when medical science had advanced to a position making them plainly untenable. Hence Rush was a great physician in good standing, while the others were excluded from regular medicine and became the founders of modern sects.

In summing up, the most serious criticism of Rush seems to be that he persisted in a traditional approach to the problem of disease, in a day when more promising procedures were already being adopted in European centers. While his reasoning was ingenious and generally consistent, his temperament and other factors were such that he pushed his approach to extremes in practice. Yet this does not mean that the praises heaped upon him were unmerited. He was, in some respects, a keen clinical observer, and note how his imagination served him in such a matter as the recognition of focal infection. His work in psychiatry has been duly appreciated in recent years, as interest in a psychological orientation in that field has revived. Here he was at his best, for the subject called only for clinical observation, and involved reasoning about matters that were abstract and obscure. His theories about local miasmas, as disease-producing stimuli in epidemics, were no more one-sided than were those of his opponents; and they had the added merit of encouraging the great sanitary reform movements which were inaugurated during his own life-time. His very indifference to laboratory research may be interpreted as the defect of his virtues; since it seems to have resulted from his earnest desire to aid suffering humanity, rather than to bury himself in investigations remote from the needs of his friends and patients. And though the influence of his "system" probably delayed such research in this country, he was only one of many clinicians who then and subsequently displayed little interest in laboratory investigations.

It has already been implied that, although Rush looked backward in his theory of disease, he was modern in the sense that certain of his eighteenth-century views have been revived during our own time. His concentration on "excessive action" in the vascular system seems analogous to the concern now accorded the whole "hypertension" complex. (Incidentally, current theories regarding this major problem still divide along much the same lines that separated the two theoretical schools of the earlier centuries; that is, between humoral and tension hypotheses.)[22] Even Rush's doctrine of disease unity had the merit of viewing the patient as a whole—a merit that was lost during much of the nineteenth century when emphasis upon specificity was carried to extremes. His concern with psychosomatic relations is an excellent illustration in this connection.

Rush illustrates, finally, two other eighteenth-century traits or practices which were largely lost thereafter, only to be revived in recent years. These relate not to physicians in particular but to scientists in general, among whom Rush—with his wide interests ranging from chemistry to psychology—would certainly have arrayed himself. The first trait was this very versatility which was so typical of many seventeenth and eighteenth century thinkers. At this point we usually think at once, in this city, of Franklin; but versatility was also characteristic of Rush, of Jefferson, of Benjamin Thompson, and of William Charles Wells—to name only some of Franklin's own countrymen. True, it was easier to be versatile when science and learning were relatively non-technical. With the growth of knowledge during the 1800's, progress seemed possible only through specialization. But

[22] See, *e.g.*, Eugene M. Landis, "Pathogenesis of Hypertension in Man", Univ. of Penna. Bicent. Conf. on *Hypertension* (Phila., 1941), 9ff.

the resulting divisions between fields must now in some way be overcome, so that something of that earlier access from one area to another may be revived. Rush's type of mind would be most helpful today in what is termed "cross-fertilization" or "the breaking down of departmental barriers."

The second practice which Rush well illustrated in his day, and for which there is now a renewed demand, was the active participation by scientists in public affairs. He considered it his duty, as a physician and an intellectual, to take part in the Revolution, and it was no accident that he became a signer of the Declaration of Independence. Although he held no major political positions, he gave himself thereafter to all sorts of social reforms. In like manner the two greatest American physicists of that era, Benjamin Franklin and Benjamin Thompson, each became an outstanding public figure; the one in his own country and the other—as an exiled Loyalist—in Bavaria.

Subsequently, something of a divorce between science and public affairs ensued. By the later nineteenth century, few scientists were active in public life, and governments took small interest in science—at least in English-speaking lands. I need not labor the point of how all this has changed of late, and of how scientists are once more becoming public figures and governments are taking them seriously—or at least more seriously than they did but a generation ago. The atomic bomb only dramatized trends which had already set in in this direction.

The moral of all this is that Rush was more modern in many ways, as a medical man and as a scientist, than we might at first suppose upon dipping into his lectures and essays. The most famous American physician of his time, he did much to establish a great medical tradition in this city. Despite scientific and human limitations, he remains a striking figure in whom Americans in general and Philadelphians in particular may well take an unaffected pride.

# Benjamin Rush's Theories on Blood Letting after One Hundred and Fifty Years*

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*Introduction*

WHEN I was invited by the College to speak at this meeting "Commemorating the Bicentenary of the Birth of Benjamin Rush," I suggested that I should play second fiddle to the main speaker of the evening, Professor Shryock, and that I should speak briefly on the limited subject of how Rush's theories and practice of bleeding look to us a hundred and fifty years later. I am quite a little embarrassed to find that my remarks are to form the fifty-ninth Mütter Lecture. The lectures in this series, endowed by Doctor Mütter, have included many of great distinction especially by surgeons and pathologists, including Dr. John Packard who delivered the first Mütter lecture eighty-two years ago. I apologize for joining this group of Mütter lecturers with a presentation intended only as a string to Professor Shryock's kite, but my subject is an interesting one and does form an important facet in the proper appreciation of the remarkable man, Benjamin Rush, whom we are honoring tonight.

That Benjamin Rush was a remarkable man of vehement and aggressive character, you must have concluded from the delightful remarks of Professor Shryock. His very nature, indeed, gave assurance of constant and acrimonious altercation and on no point was this more violent than with regard to his theories and practice of blood letting. There is no doubt about the facts concerning the amounts of blood which he removed from patients especially during the great epidemics of yellow fever in Philadelphia in 1793 and 1797, for the figures which he records with pride in his own writings, are identical with those quoted by his opponents in their accusations of him as a murderer.

There is no doubt that Doctor Rush advocated and practiced blood letting to a degree seldom, if ever, reached or exceeded by others although he himself quotes a few instances recorded in the older medical literature of the removal of even greater amounts. As was sure to be the case, there were many conservative physicians who earnestly disagreed with Rush and his methods of treatment nor did Rush's open criticism of all other treatments and his vehement support of his own, tend to allay the bitter polemic. There was a wide divergence between the claims of Rush and his followers and the derogatory statements of his antagonists.

Rush was not quiet nor was he modest in praising the benefits of the treatment with copious blood lettings and purgation. He claimed that many more patients with yellow fever recovered under his treatment than under the older use of wine, blisters and 'the bark,' as quinine was called. For example in a personal letter[1] to his wife Julia, written on September 11, 1793, Rush states "I have this day visited and prescribed for upwards of 100 patients, and have not had a single death among them. Four persons in the British minister's family will swell the triumphs of mercury, jalap and blood letting." In another letter he writes "I seldom lost more than one in twenty"—and in another place he records that "two-fifths of all of the sick that were sent to Bushkill" succumbed,—Bushkill, where his treatment was not followed, was the hospital established for the care of yellow fever victims on an estate named Bush Hill, in the vicinity of 18th and Buttonwood Streets, but Rush perhaps with unsuspected humor, spells the name Bushkill.

One can find very different statements in the bitter attacks by his many opponents. Many of them are quoted in the delightful book on Benjamin Rush by Goodman.[2] For example, Cobbett com-

* Thomas Dent Mütter Lecture LIX, the College of Physicians of Philadelphia, read at a Special Meeting of the College, November 6, 1946, commemorating the 200th anniversary of the birth of Benjamin Rush, one of the founders of the College.

[1] Old Family Letters Relating to Yellow Fever, pp. 23, 79, 100.

[2] Benjamin Rush. By Nathan G. Goodman, University of Pennsylvania Press, 1934.

paring Rush to Samson wrote—"The Israelite slew his thousands, but the Rushites have slain their tens of thousands." Rush had termed the drug mercury, "The Samson of Medicine" and this may have confused Cobbett into misquoting the biblical book of Samuel in which it is written that "Saul slew his thousands and David his ten thousands." Cobbett[3] also blamed Rush's teaching for the death of George Washington who within twenty hours was bled an estimated gallon and a pint by followers of Rush. Without taking sides at this late date, we must accept as a fact that many patients seriously ill with a dangerous fever survived what can only be termed heroic blood letting and purgation.

Before discussing Rush's practice of blood letting further, we should speak briefly of his other main stay in the therapy of yellow fever. This was purgation and to insure results he gave purgatives in what today seem like enormous doses—a powder of ten grains of calomel and fifteen grains of jalap administered not only once but repeatedly. If such a degree of purgation was obtained as to lead to bleeding from the bowel, this was considered by Rush merely to supplement the benefits obtained by the other bleedings.

Let us now return to this matter of blood letting. To appreciate just what the bleedings advocated by Rush mean in terms of our body's total blood volume, we must remind ourselves that the whole blood is about one-eleventh or 9 per cent of our body weight. In other words, the blood volume of an average sized man of normal weight will be about six liters or a little more than six quarts. Please note this amount—six quarts, for Rush did not hesitate to remove a quart at a time and to repeat this procedure two or three times within forty-eight or seventy-two hours, thus letting out a good half of the patient's total blood. He even went further than this and he wrote "Bleeding should be repeated while the symptoms which first indicated it continue, should it be until four-fifths of the blood contained in the body are drawn away." Let those of us who experienced discomforts after making a small donation of blood at the Red Cross or hospital take this to heart.

We need not labor our evidence of huge bleedings any further but certain interesting questions must be answered. How did Rush dare to go so far, and what were the reasons or indications which led him to do so? Before discussing these matters, however, let me quote from a letter written in 1797 to Rush by one of his students, Dr. John Bullus of Reading, Pennsylvania, who certainly absorbed and followed the precepts of his teacher and as may often happen, carried them even further. This letter is preserved among the Rush papers in the Ridgeway Library and was reprinted in 1944 by James E. Gibson[4] in *The General Magazine and Historical Chronicle.* It reads in part as follows:

"A few days ago I was called in consultation by three Empirics to see a woman in a case of as violent inflammatory fever as I have ever seen. I found her with all the symptoms of that disease—delirious—comatose, and with a depressed pulse—a combination which my professional brethren had never experienced before. She was also in the eighth month of pregnancy. In this situation I did not hesitate to spill a little human blood, which so startled the three men that they ran from the room —went to the husband and begged him in God's name to dismiss me that his wife's life might be saved, so I was discharged. They then administered a dose of opium and in a short time death was staring her in the face. I was immediately called back and when I found the three murderers also present, I informed the husband I would do nothing more until they were dismissed from the case, but they were finally allowed to remain on promises not to interfere with me. I then withdrew 30 ounces of blood and gave an enema. Four hours later I took 25 more ounces of blood and this raised her pulse considerably, but she continued delirious and comatose; six hours afterwards I drew 25 additional ounces which produced some regularity in her pulse. I then applied a blister to her neck and ice to her head—used the mercurial ointment and gave calomel. In the night we were all four hastily summoned to the patient and I found her pulse had sunk, but I raised it again by bleeding off 30 more ounces which so exasperated the others that they left the house and reported I had killed the woman. Greatly to their astonishment they learned the next morning that by reason of another bleeding I had given, the patient was quite out of danger and the mercury had begun to operate. Her coma and delirium had disappeared and once more she was able to converse with family and friends. Three days later, when she was in a proper state of salivation, her labor began very naturally

[3] Porcupine's Gazette, October 19, 1799, p. 62.

[4] Blood Transfusion in Reverse, James E. Gibson. *General Magazine and Historical Chronicle*, 46: 60, 1944.

and with great ease. As it continued rather long, I thought it quite proper to accelerate matters by further treatments, so I bled her twice again, which fortunately for the preservation of my reputation, had the desired effect. I had no sooner bound up her arm than I delivered her of two fine boys without any difficulty to her and with great ease to myself, as well as with scarcely any pain to my poor patient. She has since told me she had never experienced less difficulty in all the fourteen deliveries she had passed through, and should she have twenty more children, she would always be bled when in labor. My charge will not be more than ten or twelve dollars, though it ought to be three times that sum.

"Since this experience I have been engaged by two women to attend them in their expected labor. You see Sir, I have not deserted the Lancet, nor will I ever relinquish it but with my life."

Now let us consider this matter from our vantage point of a century and a half later. How dared Rush go so far? In the first place, Rush was greatly influenced by the theories of Sydenham even though that great physician had died more than a half century before Rush was born. In the teaching of Sydenham, blood letting especially in fevers was given a definite value, but he never carried bleeding to the lengths employed by Rush. In fact, Doctor Rush derived much of his medical philosophy as well as his treatment of fevers from Sydenham, although he records[5] that "My first principles in medicine were derived from Dr. Boerhaave."

We do not know just how Rush came to exceed the blood letting practice of Sydenham but his doing so is quite in keeping with the intensity of his belief in any theory once adopted. It was about 1790 that he became firmly convinced that all fevers are due to disturbances in the blood vessels, particularly in the arteries. Once convinced of this, the logic of the situation as it appeared to him, easily led him further and further for, as he wrote "In the use of this remedy it may be truly said, as in many of the enterprizes of life, that nothing is done, while anything remains to be done."

And then he was perhaps unduly influenced by a happening in a single case. This patient was bled the usual amount one evening but in the morning was found in a pool of blood which had by accident, leaked during the night from the vein opened for the blood-letting. The improvement in the condition of this woman far exceeded that anticipated from the single bleeding and Rush was quick to come to a conclusion which was so pat to his theories, that the greater loss of blood had caused the greater benefit. This seems to have bolstered his faith and justified more and bigger bleedings. After his experience in the epidemics of 1793, he increased the blood-lettings in 1794 and in the later epidemics. Soon he was honestly convinced that the results of his treatment far excelled those of others and certainly no doubts or hesitancy remained. We may think him wrong but no one can read his letters and writings and doubt his honesty, and his desire logically to apply the scientific methods of observation and deduction so strongly emphasized by Sydenham. He certainly had the strength of his convictions for when attacked by yellow fever he had himself bled twice and took a dose and a half of the mercurial medicine —perhaps a little less of each than he was used to prescribe for others. For example, Dr. Philip Syng Physick ascribed his own recovery from yellow fever to his treatment by Rush with the removal of 176 ounces of blood by 22 bleedings in ten days.

One might suggest that at the time of Rush an accurate method of measuring the amount of blood in the body was lacking and that the total blood was thought to be much greater than we now know it to be. If this were true, then perhaps Rush might have thought that he was not removing so large a fraction of the whole. In his essay entitled "A Defence of Blood-Letting" he states "that in a person of ordinary size, there are supposed to be contained between 25 and 28 pounds of blood . . ." As a check on this statement, I found on looking in the Library of the College of Physicians, at the suggestion of our Librarian, some note books of students who took the course in Physiology given by Benjamin Rush, one in 1809, another in 1813. In these notes although characteristically illegible, the total volume of blood in the average human body was stated similarly, once as 25 pounds and once apparently as 28 pounds, these figures, of course, being about twice the actual amount. Unfortunately, for this attempt to explain the large bleedings of Rush, we have his own words that "Bleeding should be repeated . . . should it be until four-fifths of the blood contained in the body are drawn away." Had he attempted to take

[5] An Inquiry into the Proximate Cause of Fever.

away four-fifths of twice the amount present there can be no doubt of the result! He did, however, believe that "much more blood may be taken when the blood vessels are in a state of morbid excitement and excitability than at any other time."

Now let us review the conditions of the pulse which, according to Rush, indicated the necessity of bleeding or of further bleeding. These he records[6] as follows:

1. A full, frequent and tense pulse . . .
2. A full, frequent and jerking pulse . . . without tension . . .
3. A small, frequent, but tense pulse . . .
4. A tense and *quick* pulse, without much preternatural frequency.
5. A slow but tense pulse . . .
6. An uncommonly frequent pulse, without much tension . . .
7. A soft pulse, without much frequency or fulness.
8. An intermitting pulse.
9. A depressed pulse.

And to complete this list which would seem to include almost every possible type of pulse our enthusiast ends with

10. An imperceptible pulse.

How could he fail to find in every patient with yellow fever or indeed any disease an indication for bleeding in the state of the pulse? Nor how could one or even repeated bleedings remove the clear indication for the taking of still further blood? Although it is true that Doctor Rush lists among the beneficial results of blood letting not only that "It reduces the uncommon frequency of the pulse" but also "It renders the pulse more frequent when it is preternaturally slow."

Although removal of such large amounts of blood was soon abandoned and indeed bleeding itself discredited—in part perhaps as a result of Rush's practice, modern science has interested itself in the effect of removal of blood on the pulse and circulation. Little has been learned which supports the claims of Rush although it must be admitted that the recent observations have usually been on normal individuals. The common belief has been that the loss of any considerable amount of blood caused a rapid pulse and a low blood pressure. This old concept has recently been proved erroneous by a group of investigators[7] at the University of Pennsylvania. They bled 18 healthy volunteers about a pint and 17 about a quart. When the larger amount was removed fainting with slowing of the pulse sometimes occurred but with the lesser bleeding there was no change in the pulse rate as long as the person remained recumbent. But the upright position often caused an increase in pulse rate and sometimes fainting. This is, of course, most important in the recognition of hidden hemorrhage which obviously may proceed in a recumbent patient without the appearance of the old criterion of a rapid pulse. These observations may explain why Rush noted that fainting "often occurred after the first and second bleedings in a fever, but in no subsequent bleeding, though it be repeated a dozen times." Perhaps after two bleedings by Rush the patients could not rise from the recumbent position!

Rush not only found indications for bleeding in the pulse but also in the state of the removed blood for he wrote[8] "after blood letting has been performed, the appearance of the blood should be attended to in order to judge of the propriety of repeating it." He noted a number of indications in the appearance of the blood in the bleeding bowl but was especially impressed by blood covered with a buffy coat. This blood was termed sizy—a word we retain in use today applied to a gelatinous material used as a first coat by plasterers and in glazing paper. The more sizy the blood the more clear the indication for bleeding, according to Rush. He was so sure of his ground in this matter; he was so careful in his observations; he was so scientific according to his lights; he was so nearly right—but time has proved him wrong for we now know that copious blood letting itself, by causing anemia, directly increases the size of the blood and so the indications for more bleeding.

Interest in this buffy layer which forms in drawn blood goes far back into early medicine. Historically, "the theoretical argument in favour of venesection . . . was founded on the conception that by emptying the vessels of their contents the organism could be relieved more or less from the materia morbificans, i.e., the substance of the

[6] Defence of Blood Letting.

[7] Shenkin, H. A., and others. On the Diagnosis of Hemorrhage in Man. A Study of Volunteers Bled Large Amounts. Am. J. Med. Sci., 208: 421, October, 1944.

[8] A Defence of Blood Letting.

buffy coat."[9] The Greeks recognized correctly that it was increased in diseased persons but explained this as due to an increase of the phlegma which was one of the four fluids of the body. Theories changed but a belief in the significance of this buffy coat or size persisted through the 18th Century. Sydenham, for example, believed in 1753 that the common cause of all febrile diseases was an inflammation of the blood and that the sure evidence of this was the sizyness of the blood. Not long after this date the true explanation of this phenomenon began to be discovered. The steps of this are interesting in themselves. The story has its beginning in 1772 in fact during the life of Benjamin Rush, when an English physician, William Hewson, observed that the most important factor in determining the amount of buffy coat or size of the blood was the rate at which the red blood cells settled down out of the liquid serum of the blood. He concluded that the size or crust was nothing more than the clotted fluid of the blood left behind as a yellowish layer after the red cells had fallen to the bottom of the bleeding bowl. This would seem to dispose of the theory held by Rush that the amount of size was an indication of the need of further treating the fever which, of course, to him meant further bleeding. But in 1786, John Hunter in his lectures taught correctly that in all inflammatory states the red cells sink more rapidly and thus are not caught high up in the clot thus leaving a thick buffy coat. We have no information as to whether Rush knew of or cared anything for these discoveries.

Nothing further of importance was learned for over a hundred years until in 1918, Fahraeus, of Sweden, restudied this phenomenon of the sedimentation or sinking of the red blood cells while he was searching for a test for pregnancy. Fahraeus approached the problem not from the point of the amount of buffy coat but by determining the rate at which the red cells sank or sedimented. It had long been known that the sedimentation was more rapid in normal pregnant women as well as in infections and in many wasting diseases. The phenomenon, therefore, is not a specific one for any single condition. Rush was partly right in using the thickness of the size as an indication of the presence of an inflammatory process; he was at fault in using this same indication for the bleeding of pregnant women for in them it is a normal or physiological manifestation of their pregnancy. Rush unfortunately did continue to advocate the long existing practice of bleeding in pregnancy and was especially impressed by the benefit obtained by blood letting from pregnant women who happened also to contract yellow fever. What Benjamin Rush did not know was that anemia of itself increased the sedimentation rate and, of course, the sizyness of the blood. Each blood letting, therefore, paved the way for another, for each removal of blood made the patient more and more anemic.

Modern medicine no longer holds the theories about fevers so earnestly believed by Rush nor does it find an indication for bleeding in the many varieties of pulse. Yet today blood may be removed when the heart is failing and the lungs are engorged with blood; venesection or blood letting also may be done when the blood pressure is too high or when there is an excessive volume of blood in the body. Our reasons are somewhat different and our measures much more moderate—seldom more than a pint is taken nor is this bleeding repeated except at intervals of at least several days. Anemia which must have always been caused by the blood lettings of Rush, is today accepted as a distinct contraindication to bleeding. Nevertheless we do take blood when the circulation presents certain abnormalities. Nor does medicine today find an indication for venesection in the appearance of the drawn blood; we do not try in this fashion to remove the materia morbificans. And yet of late years a method of bleeding reminiscent of this theory and of Rush has been introduced. In certain poisonings and in infants jaundiced as a result of incompatibilities of the Rh or Rhesus factor of the parents, the attempt is made to remove not merely the four-fifths of the body's blood as approved by Rush—but all of it! Of course, there is this slight difference in that in this so-called exsanguination-transfusion method an amount of normal blood equal to that removed is simultaneously introduced into another vein, thus leaving the blood volume unchanged. Perhaps Rush was on the right track if only the method of replacement transfusion had been available.

From our vantage point of a century and a half later it is dangerously easy for us to criticize the efforts of Rush to be as scientific as possible in the light of the knowledge of his day. Granting his sincere belief in the theory of fevers and his ac-

[9] Fahraeus.

curate observations on the increased thickness of the buffy coat, one can sympathetically understand that logic drove him inevitably to his conclusions and his practice. Rush is by no means the only great figure in the history of medicine to follow headlong serious errors logically based on incorrect but supposedly scientific certainty. The greater the man, the more influential and harmful his error. The great Virchow, for example, delayed many years the advance of medical knowledge by putting his vast authority behind an erroneous theory of the metastasis or spread of tumors. Hebra, the great dermatologist, did likewise with his insistence in the last century that chickenpox was not a separate disease but actually a mild form of smallpox. More than likely we are committing the same type of mistake today—perhaps following some misguided leader or with complete self-satisfaction, ordering our practice on some now accepted but soon to be disproved, theory.

It is healthy for us, therefore, today to reconside these old theories and practices of Benjamin Rush to see why he was so sure; to realize how good th scientific evidence of his time seemed to him Perhaps he came nearer to the truth than we think perhaps a century from now exsanguination bleed ing plus transfusion will have a larger place in ou therapy. None of us can do more than to prac tice the accepted science of our day and if fortunat to be one of the few to advance it some little. A review of Rush's practice with its seeming excesse should not lead one to a thoughtless condemnatio of him but on the other hand, to a greater admira tion of him. He was courageous, he was stubborn but he tried to be meticulously scientific. He wa opinionated and hot-headed and perhaps woul have been mellowed somewhat by an occasiona copious blood letting. Much has been said an written of Benjamin Rush but the best estimat of him is that of Samuel Jackson of Northumber land who wrote of Rush that he was "wonderfully entangled in the web of his honest sophistry."

# Benjamin Rush's Apprenticed Students

*By* JAMES E. GIBSON

*Philadelphia, Pa.*

INCLUDED among a number of unrelated subjects in a notebook indexed under "Facts and Observations", Dr. Benjamin Rush recorded some names and residences of medical students who received individual training in his "shop" (1).

This entry was undoubtedly made in the year before Rush's death, for it began with students who registered in 1812 and continued in a backward yearly sequence until the last page of the list contained the names of those who came under Rush's direction in 1770, the first year of the doctor's established practice.

There is a justifiable suspicion that the record is not a complete roster of Rush's apprentices, for twice there is a lapse of three years in his record. One of these intervals is between the years 1775 and 1778, and yet on July 30th, 1776, Rush wrote his wife: "I shall have a regiment of prentices, having had an application this day from a lad in the Jerseys—but the Jews house in the Alley will make an excellent Barrack for them. I am pleased with taking Jonny Pintard into the house. I suppose you told him the fee was 100 guineas. This sum with what we have by us, and what I expect soon to receive, will enable us to realize our money in a house or a plantation."(2)

Rush's apprentices lived as part of his family to the extent of the house's capacity, while the overflow lodged near by.

It is probable that some of Rush's recorded list was copied from notes in his possession, for it contains several specific dates, with comments on certain individuals that it is unlikely he could have retained in his memory. It is significant, however, that 26 of the 135 mentioned were entered without given names, while some family names were misspelled. A few of these omitted first names, as well as corrections in spelling, were found in letters among the Rush manuscript collection. Many of these communications told of difficult cases the young physicians—former apprentices of Rush—were encountering, and ended with requests for advice as to proper medicines and treatment. Others expressed discouragement and doubts as to whether they had chosen the right neighborhood in which to begin practice. Many told of local opposition against the throes of bleeding their preceptor had taught them. Some were just friendly letters, inquiring for Rush's health and that of his family; asking for news of other apprentices and expressing sincere admiration and affection for their old "master". Quite a number of these epistles contain material of historical value, with possibilities of interesting articles. All these letters required, and probably received, replies, but unfortunately Rush did not retain many copies, though he always recorded his professional recommendations in notes on the back of the original inquiry. These should prove of great value to any medical man seeking information on the treatment of disease in the early days of the Republic.

Rush evidently kept informed of his old students, though they were located far and near, for on July 5th, 1800 he recorded that 22 of them had died. Six years later, he added 6 more to the list of those who had passed away, checking off their names with an 'X'.

Many letters are on file containing inquiries for Rush's terms and conditions for apprentice training, and they furnish evidence that only a small percentage of them received serious consideration. His selections were carefully made and were often from among sons of personal friends, though he seemed always willing to accept candidates recommended by his old students. Some of the men Rush received had already served an apprentice-ship with a physician in their home locality and a few had even experienced a period of practice, but they seemed to reason that additional training with opportunities to attend lectures at the University of Pennsylvania and clinics in the Pennsylvania Hospital would increase their medical knowledge and prestige when they began or resumed professional activities.

A number of Rush's students continued their studies in the hospitals and universities of Europe with letters of introduction and commendations from their Philadelphia preceptor. Their letters written to Rush are full of comments on the pro-

fessional men whose lectures they were attending, with observations of some differences between American and foreign theories and practices. James Hall, one of these students, was financed in this post-graduate work by his old "master", and after obtaining his diploma at Edinburgh he returned to Philadelphia to be accepted as a partner in Rush's medical office (1).

Some of Rush's graduated apprentices sought appointments in the Medical Departments of the Army and Navy (1). At least four of them were commissioned and served with the United States fleet during the Quasi-War with France and continued in that service for the conflict with the Barbary Pirates in the Mediterranean (3). The experiences of one of these, Dr. John Bullus, have already been recounted (4), and the letters and Government records of the other three—Rush's son John, Daniel Hughes and Samuel Marshall—contain much heretofore untold history.

The names and records of 15 of Rush's listed apprentices may be found in the roster of medical men who served with the armed forces in the Revolutionary War (5), though one of them was included not because of professional aid but rather because of activity as commander of troops through the ranks, respectively, of captain, major, and colonel. He was John Beatty, of Bucks County, Pennsylvania. After the war, he established a medical practice in New Jersey, near Princeton, and served his adopted State in several important public offices.

James McHenry, after acting as a regimental surgeon and on the staff of an army hospital, joined Washington at Valley Forge as a personal secretary. Upon the election of Washington to the presidency, McHenry was made Secretary of War and continued in that capacity through Adams' first term.

Enoch Edwards, of New Jersey, served as surgeon of New Jersey troops; James Tate, of Pennsylvania, was surgeon of the 3d Pennsylvania Regiment, and was among those who took the Oath of Allegiance at Valley Forge. Abel Morgan, of Pennsylvania, also served at Valley Forge and likewise subscribed to the Oath required of all commissioned officers.

James Dunlap, of Pennsylvania, was a surgeo in the navy, while Andrew Leiper, also of Pennsyl vania, is mentioned as having treated the wounde at Brandywine. James Finley served as medica officer in several Massachusetts regiments an remained in the army until Nov. 3, 1783. Andrew Todd, of Pennsylvania, was a navy surgeon, whil Wilson Waters is recorded as a surgeon's mate i an army hospital of the Middle Division.

John Rodgers, of Pennsylvania, was attache to the 1st Pennsylvania Regiment as its surgeon Michael Leib, of Pennsylvania, is simply men tioned as having attended sick and wounded sol diers, but it is not told where or in what capacity John McConnell, of Pennsylvania, is listed a a surgeon in one of the Philadelphia army hos pitals. Gilbert Tennent, of Pennsylvania, i known to have been attached to one of the out lying hospitals of the Valley Forge Encampmen located at French Creek, while Jacob Tobin, o Delaware, served in the same hospital—both a surgeon's mate.

Rush's penmanship in this instance was ofte confusing, permitting two or more interpretations and though examined under a powerful readin glass, a few errors may have been made. The lis as given below records the names of the appren tices, first, in alphabetic order, rather than in th chronologic sequence used by Rush; then, in geographic classification. The entry name is i the established spelling as known to the autho Following it appears the name as Rush wrote it except that his abbreviations of given names hav not been retained where the full name is known names or other matter supplied by the autho from other sources appear in brackets. The othe data are given in a consistent order. Rush' own comments appear in quotation marks. A remaked above, he drew a cross against the name of apprentices who were known to him to be dead sometimes adding the word "dead". Where bot the cross and the word appear, only the word ha been quoted; in other cases, the cross in quotatio marks carries the same significance.

Notices of errors, or of omissions in Rush's lis will be welcomed by the author.

BENJAMIN RUSH'S LIST OF HIS APPRENTICES

| | | | |
|---|---|---|---|
| Alexander. | Ashton Alexander. Virginia. April 16, 1794. | Alston. | William Alston. S. Carolin Nov., 1794. |
| Alston. | John Alston. S. Carolina. 1792. "Dead." | Anderson. | James Anderson. Marylan June, 1795. |

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|---|---|
| Annan. | Robert Annan. Pennsylvania. 1787. |
| " | William Annan. Pennsylvania. 1787. "Dead." |
| Atchinson? | Atchinson. New Jersey. 1812. |
| Bache. | Franklin Bache. Phila. 1811. "3 years." |
| Barnhill. | Barnhill. Phila. July, 1811. "3 years." |
| Bayerton. | George Bayerton. [Maryland.] 1790. "Dead." |
| Beatty | John Beatty. Pennsylvania. 1770. "Idle but worthy." |
| Bellinger. | John Bellinger. S. Carolina. June 15, 1795. |
| [Birckhead.] | Solomon Birchead [Birckhead]. Maryland. 1780. |
| [Brackett] | Bracket [Joshua Brackett]. New Hampshire, 1799. |
| Brown. | Thomas Brown. New Jersey. Dec., 1795. |
| [Brundidge?] | Henry Brundage [Brundidge?]. Virginia. March, 1812. |
| Bryan. | [Guy] Bryan. Pennsylvania. 1802. |
| Bullock. | George Bullock. Phila. 1805. |
| Bullus. | John Bullus. New Jersey. 1793. |
| Campbell. | Campbell. Virginia. June, 1811. |
| Chamberlain. | Samuel Chamberlain. Maryland. 1781. "Dead." |
| Chapman. | Nathaniel Chapman. Virginia. March–April, 1799. |
| Claypoole. | William Claypoole. Phila. 1778. "Dead." |
| Cock. | Samuel Cock. Virginia. 1797. |
| Cocke. | Charles Cocke. Virginia. 1805. |
| Coxe. | John Redman Coxe. Phila. 1791. |
| " | Swepson Coxe. S. Carolina. May, 1809. "One year." |
| Croghan | J[ohn] Cro[?]an [Croghan]. Kentucky. Dec., 1809. "3 years." |
| Delion. | Delion. S. Carolina. April, 1810. |
| Dick. | Elisha [Cullen] Dick. Delaware. 1780. "Left me without leave, and went to Dr. Shippen." |
| Dickinson. | Nathaniel Dickinson. New Jersey. Nov. 5, 1802. |
| Dill. | Armstrong Dill. Pennsylvania. 1785. "Dead." |
| Dunlap. | James Dunlap. Pennsylvania. 1771. |
| Earle. | Earle [son of Caleb Earle]. Phila. 1811. |
| Edmonds. | [Carter?] Edmonds. Virginia. 1797. "Dead." |
| Edwards. | Enoch Edwards. Pennsylvania. 1770. "Idle, acute—afterwards industrious & respectable." |
| " | Isaac Edwards. Virginia. Aug., 1795. |
| Eversfield. | Charles Eversfield. Maryland. 1804. |
| Finley. | James E. B. Finley. Pennsylvania [Massachusetts?] 1775. |
| Fisher. | Edward Fisher. Virginia. 1791. |
| Ford. | George Ford. S. Carolina. April, 1795. |
| Fuller. | [Thomas] Fuller. S. Carolina. Nov., 1807. |
| Gauntt. | Edward Gauntt. Maryland. 1809. |
| Goldsborough. | William Tighlman Goldsborough. Maryland. 1786. "Dead." |
| Gough. | John Parker Gough. S. Carolina. April 21, 1796. |
| Grey. | George Grey [line drawn through name]. Phila. Aug., 1810. "Went away." |
| [Griffith?] | Alexander [L.] Griffitts [Griffith?]. Maryland. Nov., 1809. "3 years." |
| Hadley. | John L. Hadley. N. Carolina. March, 1811. |
| Hall. | Elisha Hall—"son of Elisha." Maryland. 1771. |
| " | Elisha Hall—"son of Elihu." Maryland. 1781. |
| " | James Hall. Maryland. 1779. "X." |
| " | Thomas Hall. Maryland. May, 1811. |
| Handy. | Hast Handy. Maryland. June, 1789. |
| Hawkins. | Hawkins. Maryland. 1811. |
| Hayne. | Isaac Hayne. S. Carolina. 1782. "X." |
| Heberton. | John Heberton. Phila. Aug., 1810. "3 years." |
| Hinchman. | Js. Hinchman. 1775. "Died in the first year of his studies." |
| Horsey. | William Horsey. Maryland. 1801. |
| Hoskins. | [John?] Hoskins. N. Carolina. March, 1808. |
| [Hughes.] | Daniel Hews [Hughes]. New Jersey. March, 1797. |
| [Jenks.] | Phineas Jinks [Jenks]. Pennsylvania. 1801. |
| Johnson. | Js. Johnson. S. Carolina. March, 1810. |

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|---|---|
| King. | Thomas King. Maryland. 1797. |
| Lehman. | Lehman. Phila. 1808. |
| Leib. | Michael Leib. Phila. 1778. |
| Leiper. | Andrew Leiper. Maryland. 1771. "Dead." |
| Luffland. | James Luffland. Delaware. 1810. "3 years." |
| [McClellan?] | John McCleland [McClellan?]. Pennsylvania. 1785. |
| McClen. | Joseph McClen. Virginia. July, 1809. |
| McConnell. | John McConnell. Pennsylvania. 1782. "Dead." |
| McHenry. | James McHenry. Ireland. 1771. |
| [McLane.] | [Allen] McClane [McLane, Jr.]. Delaware. Nov., 1807. |
| Manners. | John Manners. New Jersey. 1808. |
| Marshall. | [Samuel] Marshall. Barbadoes. 1796. |
| May. | Alexander May. Pennsylvania. March–April, 1799. "Dead." |
| Mayo. | [Robert?] Mayo. Virginia. 1802. |
| " | " " " 1807. |
| Mease. | James Mease. Phila. 1789. |
| Miram? | Miram?. Delaware. 1805. |
| [Mitchell.] | Edward Mitchill [Mitchell]. S. Carolina. July 19, 1809. "For one year." |
| Montgomery. | William Montgomery. Pennsylvania. 1779. "X." |
| Morgan. | Able [Abel?] Morgan. Pennsylvania. 1771. "Dead." |
| Morris. | Cadwalr. Morris. Pennsylvania. 1779. "Dead." |
| " | Morris. Pennsylvania. March, 1812. |
| Mosely. | Mosely. Virginia. 1803. |
| " | Mosely. Maryland. March, 1808. |
| [Muhlenberg?] | [Frederick A.?] Muhlenburg [Muhlenberg?]. Lancaster, Pa. Oct., 1811. "3 years." |
| [Murdock] | Jonathan Murduck [Murdock]. Pennsylvania. 1802. |
| Murray. | George W. Murray. Pennsylvania. 1808. |
| Otto. | John [C.] Otto. New Jersey. 1792. |
| Peachy. | John Peachy. Virginia. 1780. "Dead." |
| Porter. | John Porter. Phila. 1778. |
| Potter. | Nathaniel Potter. Maryland. 1790. |
| Poyntell. | George Poyntell. Phila. 1804. |
| Proudfit. | James Proudfit. New Yorl 1787. |
| Pugh. | Whitman Pugh. Virginia. 180 |
| Ramsay. | William Ramsay. Marylan 1775. |
| [Rees?] | Reece? [John T. Rees?]. Mar land. 1802. |
| Reynolds. | John Reynolds. Pennsylvani 1806. |
| Rice. | John Rice. Ireland. 1810. " months." |
| Roan. | Thomas Roan. New Jerse March–April, 1799. |
| Robinson. | Robinson. S. Carolina. May, 181 |
| Rodgers. | John Rodgers. New York. 177 |
| Rudder. | Philip Rudder. Barbadoes. 179 |
| Rush. | James Rush. Phila. 1805. |
| " | John Rush. Phila. Sept., 179 |
| [Sammer?] | [Sammer?]. Pennsylvani Nov., 1807. |
| Sayre. | Francis B. Sayre. New Yorl 1787. "Dead." |
| " | [John] Sayre. New York. 180 |
| Slaughter. | Slaughter. Virginia. Nov., 181 |
| Smyth. | Leopold Smyth. Georgia. Jul 1798. "Dead." |
| Sommerville. | George Sommerville. Marylan 1775. "X." |
| Stall. | John Stall. Pennsylvania. 179 "Dead." |
| Stevenson. | John Stevenson. Phila. 1771. |
| Stock. | John Edmonds Stock. Englan 1797. |
| Stockett. | [Richard Galen] Stockett. Mar land. July 26, 1797. |
| Sutherland. | Joel B. Sutherland. Phila. Aug 1810. |
| Tate. | James Tate. Pennsylvania. 177 "Idle—but successful." |
| Tennent. | Gilbert Tennent. Pennsylvani 1775. "Drowned in the ge Sinclair in the year 1780." |
| Tindall. | [P. B.] Tindall. [Virginia.] 181 |
| Tobin. | Jacob Tobin. Delaware. 177 "Dead." |
| Todd. | Andrew Todd. Pennsylvania. 177 |
| Tongue. | James Tongue. Maryland. 179 |
| Tucker. | Edmund Tucker. S. Carolin 1806. |
| [Van Brakle.] | Samuel [H.] Van Brekel [Va Brakle]. St. Croix. 1807. |
| Washington. | Warner Washington. Virgini 1790. "Dead." |
| [Waters?] | John [Waters?]. Marylan Nov., 1799. |

| | | | |
|---|---|---|---|
| Waters. | Nath. Waters. Maryland. 1807. | Woodhouse. | James Woodhouse. Phila. 1787. |
| " | Wilson Waters. [Maryland.] 1775. | Young. | Benjamin Young. Pennsylvania. 1784. "X." |
| Watson. | Gilbert Watson. Pennsylvania. 1793. "Dead." | " | John Young. Phila. 1787. "X." |
| Williams. | Williams. Pennsylvania. 1812. | | |

## Geographic Distribution

### American colonies and States

*Delaware*

Dick, Elisha.
Luffland, James.
McLane, Allen, Jr.
Miram ?
Tobin, Jacob.

*Georgia*

Smyth, Leopold.

*Kentucky*

Croghan, John.

*Maryland*

Anderson, James.
Bayerton, George.
Birckhead, Solomon.
Chamberlain, Samuel.
Eversfield, Charles.
Gauntt, Edward.
Goldsborough, W. T.
Griffith, A. L.
Hall, Elisha (son of Elisha).
" " (son of Elihu).
" , James.
" , Thomas.
Handy, Hast.
Hawkins.
Horsey, William.
King, Thomas.
Leiper, Andrew.
Mosely.
Potter, Nathaniel.
Ramsay, William.
Rees, J. T.
Sommerville, George.
Stockett, R. G.
Tongue, James.
Waters (?), John.
Waters, Nath.
" , Wilson.

*New Hampshire*

Brackett, Joshua.

*New Jersey*

Atchinson.
Brown, Thomas.
Bullus, John.
Dickinson, Nathaniel.
Hughes, Daniel.
Manners, John.
Otto, J. C.
Roan, Thomas.

*New York*

Proudfit, James.
Rodgers, John.
Sayre, Francis B.
" , John (?)

*North Carolina*

Hadley, John L.
Hoskins, John (?).

*Pennsylvania*

Annan, Robert.
" , William.
Bache, Franklin.
Barnhill.
Beatty, John.
Bryan, Guy.
Bullock, George.
Claypoole, William.
Coxe, J. R.
Dill, Armstrong.
Dunlap, James.
Earle, (son of Caleb).
Edwards, Enoch.
Finley, James E. B.
Grey, George.
Heberton, John.
Jenks, Phineas.
Lehman.
Leib, Michael.
McClellan, John.
McConnell, John.
May, Alex.
Mease, James.
Montgomery, William.
Morgan, Abel.
Morris, Cadwalr.
Morris.
Muhlenberg, F. A. (?)
Murdock, Jonathan.
Murray, George W.
Porter, John.
Poyntell, George.

*Pennsylvania—Cont.*

Reynolds, John.
Rush, James.
" , John.
Sammer(?)
Stall, John.
Stevenson, John.
Sutherland, Joel B.
Tate, James.
Tennent, Gilbert.
Todd, Andrew.
Watson, Gilbert.
Williams.
Woodhouse, James.
Young, Benj.
" , John.

*South Carolina*

Alston, John.
" , William.
Bellinger, John.
Coxe, Swepson.
Delion.
Ford, George.
Fuller, Thomas(?)
Gough, John P.
Hayne, Isaac.
Johnson, Js.
Mitchell, Edward.
Robinson.
Tucker, Edmund.

*Virginia*

Alexander, Ashton.
Brundidge, Henry.
Campbell.
Chapman, Nath.
Cock, Samuel.
Cocke, Charles.
Edmonds, Carter(?)
Edwards, Isaac.
Fisher, Edward.
McClen, Joseph.
Mayo, Robert(?)
Mosely.
Peachy, John.
Pugh, Whitman.
Slaughter.
Tindall, P. B.
Washington, Warner.

BRITISH ISLES

McHenry, James. Ireland.
Rice, John. Ireland.
Stock, John Edmonds. England.

WEST INDIES

Marshall, Samuel. Barbadoes.
Rudder, Philip. Barbadoes.
Van Brakle, Samuel H. St. Croix.

NO ADDRESS RECORDED OR SUPPLIED

Hinchman, Js.

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3. Office of Naval Records, Library, Washington, D. C.
4. *Transactions & Studies of the College of Physicians of Philadelphia*, 4. ser., v. 12, no. 3, Dec., 1944.
5. Duncan, L. C. Medical Men in the American Revolution, 1775–1783. Carlisle Barracks, Pa Medical Field Service School, 1931. (*Army Medical Bulletin*, no. 25); Gibson, J. E. Dr. Bod Otto and the Medical Background of the America Revolution. Springfield, Ill., Thomas, 1937.

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Philadelphia 44, Pa.

# Memoir of Joseph McFarland

*By* STANLEY P. REIMANN

JOSEPH McFARLAND was born in Philadelphia on February 9, 1868 and died suddenly September 22, 1945. His life time covered a very important span of years in the history of medicine. Bacteriology was born as a science, went through adolescence and grew up. Pathological anatomy became the efficient hand maiden of clinical medicine. Asepsis was introduced not only into surgery but into all medicine. The etiology and the method of spread of numerous infectious diseases were discovered and means to combat them were developed. Public health services took on another and different meaning during his life time. The prevention of disease began to receive the attention it deserved and which previously had been recognized as desirable but which could not be put into effect on account of lack of exact knowledge of the basic principles. Virchow had come into his own and there occurred the rise of schools of great pathologists who delved into the manifestations of diseases, catalogued various pathological processes, related and correlated them, without which pathological physiology could not have made the strides it has. Indeed, many a physiological process was clarified by a study of the pathology as it occurred, not experimentally, but naturally, so to speak, in the human beings whom the pathologists studied. The administrative phase of medicine was given great impetus by the ever-increasing success of treatment. There arose great hospitals and older ones became better operated and better equipped for the care of their charges.

In all these fields Dr. McFarland made his influence felt. His interest in science began very early and never ceased until his labors were brought to a close. The University of Pennsylvania graduated him in medicine in 1889. At that time, as before and now, there were great teachers in this medical school and among them was William Osler. No need to rehearse the interest of Osler in pathology. He advised the young graduate, McFarland, to study pathology as a back-ground for future work in any branch of medicine which he might practice, but Dr. McFarland stayed in pathology to the enrichment of that branch of medicine.

As many another young man of his days, he went to Germany for post graduate study. Working with Julius Arnold and Paul Ernst in Heidelberg and then continuing his studies in Vienna he received a thorough background training in pathological anatomy. Bacteriology was also one of his studies, as indeed the principles of it must be today for every pathologist, and for this he worked in Frankel's laboratory at Halle. His acquaintance with Virchow dated from that time and he often told about the doings of this master.

Coming back to his Alma Mater he began as assistant in pathology to John Guiteras. Soon he was given a higher appointment and then married Virginia Kinsey in 1892. Those of us who knew Dr. McFarland well know of the love and respect he had for his good wife which lasted through the years even to their golden wedding celebration.

In those days there was a Philadelphia Polyclinic Hospital combined with a Graduate School in Medicine. Dr. McFarland became Professor of Pathology in this institution but resigned soon after to begin teaching bacteriology. At the University of Pennsylvania he gave formal lectures in the subject.

About this time the epoch-making discovery of diphtheria anti-toxin was made and Dr. McFarland was instrumental in developing commercial methods for the manufacture of anti-diphtheritic serum. This was at the H. K. Mulford Company. Can anyone assess the value of these beginning efforts which through the years have saved so many lives and resulted in the present day anti-toxin? Another firm, Parke, Davis & Company, needed a consultant and Dr. McFarland became that and acted in this capacity for ten years.

The Medico-Chirurgical College was organized and for twenty years Dr. McFarland was Professor of Pathology and Bacteriology in that institution. We notice that he filled both chairs, bacteriology and pathology. Separated subjects now in most medical schools, at that time the relationships were so obvious and the bacteriological knowledge not too detailed, that one man could encompass the immediate details of both subjects. The relationships between bacteriology

and pathology are, of course, still obvious but the detailed knowledge in both subjects has increased so tremendously that it is hardly possible to be expert in both.

In 1916 the Medico-Chirurgical College was amalgamated with the University of Pennsylvania and Dr. McFarland then became Professor of Pathology in the latter institution. On many an occasion Dr. McFarland has told his friends, his colleagues and his students that this was the happiest period of his life. Those of us who knew Allen J. Smith and worked with him can well believe it, for to work with Dr. Smith was a joy, a privilege and an inspiration to everyone.

Still another medical school had the honor of Dr. McFarland's connection and that was the Woman's Medical College where he succeeded A. O. J. Kelley, himself an able clinical pathologist.

Dr. McFarland's lectures were clear and lucid, his choice of English and his method of delivery so instructive and delightful that he was in constand demand as a speaker. He gave of his talents to the veterinary and dental schools in the University and later in Temple University Dental School where he was made Professor of Pathology.

In the latter part of his life he became associated with the American Oncologic Hospital as pathologist and there he came in contact with a pronounced clinical slant. He absorbed it rapidly and his knowldge of the fundamentals which he brought to bear on clinical problems was such as to make him a most valuable consultant in that hospital and to its tumor clinic.

Like most pathologists in Philadelphia he served the Philadelphia General Hospital (Blockley) and again his experience, his clear, lucid way of explanation and his vivid description of pathological changes were a delight and a real stimulus to his colleagues, his assistants and his students.

Dr. McFarland liked to do other things than medicine. A number of us remember his showing us some of his water color sketches and the pleasure he derived from them was a delight to see. He was fond of music, too, and we saw him at various concerts and recitals. He was a member of many scientific societies, the American Medical Association, the College of Physicians of Philadelphia, the American Association of Pathologists and Bacteriologists, the American Society of Clinical Pathologists, and others. He served as president of a number and again, his interest being stirred, he served on various committees, his wise counsel to the point and dependable. As curator of the Mütter Museum of the College of Physicians of Philadelphia he unearthed many interesting acquisitions and a number of interesting papers and reviews appeared from his pen from material gathered in this Museum.

Dr. McFarland was interested in theological problems for many years. For a long time before his death he was an active member of the Unitarian Society of Germantown. He preached a number of sermons in this and other churches and again his wise counsel was felt in church matters.

The younger pathologists, not only in Philadelphia but in many parts of the country, constantly called upon him for help in the diagnosis of pathological specimens. Never did one of them call on him in vain. To those who lived in Philadelphia, when different microscopic sections were discussed, the question never failed to be asked, "What does Uncle Joe think about it?" Uncle Joe was the loving designation by which he was known to all of his confreres, colleagues and students who got to really know him. His word was good, his judgment excellent. He never said "It is a so and so because I say so" but always gave reasons for his opinion and when asked questions would launch into descriptions couched in such vivid language that one could almost see the slide from his choice of words.

Many of us, following closely his illuminating work on mixed tumors of the salivary glands, will remember the little game he put up on his brother and sister pathologists. This story also illustrates his sense of humor which came to the surface and added much to his companionship. He had a collection of several hundred microscopic slides of mixed tumors of the salivary glands. When one of the pathologists would come to him for an opinion on a slide he would say, "If you have a few spare moments look at a few slides I have and give me your opinion as to whether or not the salivary gland tumor that you examine will recur and will or will not produce metastases." So he passed out one after another of slides and we guessed yes or no. Meanwhile an amused smile grew broader and broader until at the end of fifty or more slides he said, "Well now we will look them up and see what actually happened." Referring to the careful follow-up notes of his patients, he would total the answers, break into a broad grin

and say, "Well, you were 50 per cent right and 50 per cent wrong. You might just as well have tossed a coin. You are not as good as Dr. So and So, who was 48 per cent wrong and 52 per cent right." Upon being pressed he would tell you of the difficulties of prognosis in these particular types of tumor, would tell of the attempts at treatment that had been made, some over a period of thirty or more years, and of course end up with the observation that we still need to know much more about this tumor, and all others for that matter.

Upon his death, medicine lost a very great contributor through a period of great medical activity. Medicine lost an inspired teacher, one who was born to teach and who cultivated the best methods of doing it, and many, many people lost a very good friend whose memory will linger on in the thoughts of his colleagues, his assistants, his students and many others, for years to come.

TRANSACTIONS & STUDIES

*of the*

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# President's Address*

*By* J. PARSONS SCHAEFFER

THE Ordinances and By-Laws of the College of Physicians of Philadelphia direct that the President of the College shall deliver an annual address at the Stated Business Meeting in January. This directive may be interpreted to mean that a report reflecting the general state of the College and its activities during the past year be presented. At the outset it is a pleasure to say that the College has had a successful year in the furtherance of scientific medicine, in bringing about good fellowship and coordination in the medical field in Philadelphia and its metropolitan area, and in effecting better public relations. Your President feels greatly indebted to the members of Council, the Elective and Appointive Standing Committees, the Prize and Lectureship Committees, all Special Committees, the Trustees of special College Funds, and the employees of the College occupying important positions, for their sustained interest and work throughout the past year in behalf of the College.

The total Fellowship of the College numbers 751 (as of December 17, 1946), of which 702 are Resident Fellows and 49, Non-Resident Fellows. In addition there are three Foreign Honorary Fellows, three American Honorary Fellows, and two Honorary Associates. Special College privileges have been granted a group of 16 investigators.

Membership in the Sections of the College is as follows: Ophthalmology, 58; Otolaryngology, 55; General Medicine, 144; Public Health, Preventive and Industrial Medicine, 36; Medical History has made no report. (The activities of this Section were suspended during the period of the War but will again be resumed.)

During 1946, 26 new names were added to the roll of Resident Fellows.

The College of Physicians has suffered great loss through death of one Foreign Associate Fellow, one Non-Resident Fellow, and ten Resident Fellows, during the year. All of these Fellows were greatly interested in the welfare of the College and some gave distinguished service in promoting special branches of medicine. Your President feels saddened in recording the names of the Fellows who have passed from us, and in honor of their memory would ask the Fellows of the College here assembled to stand during the reading of the names of the deceased.†

*Foreign Associate Fellow*

Edward Archibald

*Non-Resident Fellow*

Mazyck P. Ravenel

*Resident Fellows*

Charles C. A. Banes
John T. Carpenter
Daniel Louis Dozzi
William Evans
William J. MacMurtrie
F. Hurst Maier
Marion Hague Rea
Robert P. Regester
John Semple Sharpe
Joseph Walsh

* Read at the Business Meeting of the College, January 8, 1947.

† For dates, see necrological list, p. 171.

It is gratifying to report that the College of Physicians was enabled to meet all of its budget commitments and appropriations voted by Council in December 1945 and approved by the Fellows at the annual Business Meeting of the College in January 1946. These appropriations provided for the many usual and required activities of the College during the fiscal year. In addition it was possible to care for certain repairs and replacements in the College Building: the ceilings and walls of the Periodicals Room, of the Reading Room, and of the second floor hallway were renovated and painted, and all of the floors of these divisions of the College were reconditioned. A large number of the chairs in the main Halls of the College were newly upholstered. Certain plumbing repairs and replacements were required. Then, too, a much-needed, full-time assistant clerk was employed, and the salaries of a few employees were moderately increased.

The Finance Committee is to be commended for its constant oversight with reference to the financial affairs of the College, and the Hall Committee, for its interest in the College Building and its equipment and the attention it has given the many matters referred to it for consideration and report.

Although the foregoing report might be taken to mean that the College of Physicians is amply provided with income to care not only for the usual requirements but also for maintenance and emergency needs that constantly arise, this, unfortunately, is not the case. There is an urgent and immediate demand for additional income so as to enable the College to aid more adequately the Library. Every effort must be made to keep our great Library at the forefront of medical libraries, a position it has held for a great many years. The increased costs of the foreign journals, periodicals and books and the heavy charges for binding have brought new financial difficulties. Then, too, the College should increase the salaries of certain employees, long overdue, one or two men should be added to the janitorial staff, and provision must be made to care for certain repairs and replacements in and about the College Building. All of these matters are now receiving attention, their accomplishment is not insuperable and there is no reason for alarm. What is, however, needed is the interest of every Fellow of the College. Perhaps voluntary contributions are the answer or in lieu of this, a moderate increase in the regular annual contribution. Your President is certain that a way will be found which will enable the College to continue its growth and influence unabated, forward and upward.

The College of Physicians and the Philadelphia County Medical Society during the past year again united their efforts in the interest of scientific programs. Stated scientific meetings were held in the College and in the County Society Halls from January 9 to December 4, 1946. Eight joint lectures were given, two by Philadelphia physicians and six by visiting speakers from outside. All of the lectures were well attended and in some instances capacity houses received the speakers.

Your President feels that a helpful and coordinating spirit has come into being between the College of Physicians and the County Medical Society because of this joint effort during the war period in the furtherance of scientific medicine. Because of this result all concerned will, perhaps, feel loath to return to the practice of former days. Both the College and the County Society will soon be required to give attention to scientific programs for next year and the question of joint or individual scientific meetings after this academic year must first be decided.

It would appear fairly definite that both the College of Physicians and the County Medical Society have peculiarly individual fields to serve, notwithstanding that both groups are interested in the promotion of higher standards, better medicine, improved public relations, and equitable and adequate health laws. In the approach to these problems, one sees peculiar requirements for the College of Physicians as well as for the County Medical Society with reference to the type of scientific and practical programs to be presented, in carrying forward the real purposes of the individual organization, and in making stronger and better the outstanding individual assets. It may properly be argued that if too much time is consumed in a common effort the peculiar functions and opportunities and responsibilities of the College of Physicians will fail of the greatest accomplishments possible. The same may be said for the Philadelphia County Medical Society.

Having in mind the two important problems involved in the decision, I would suggest to the governing bodies of the College and the County Medical Society for consideration that two joint scientific meetings be held during the coming academic year, one in the Hall of the College of Physicians and one in the County Medical Society Building, and that all other scientific meeting

be returned to the status of individual programs. My feeling is that the method, if adopted, would continue the helpful and coordinating spirit that now exists between the College and the County Society yet, in a large measure, would return both organizations to the plan of individual programs as in former days.

Even should individual programs again be ordered by the two organizations, the good fellowship, the interchange of ideas, the visitations back and forth, and the willingness to be mutually helpful should and doubtless will continue. What advantages have been gained during the past years need and should not be lost. The College of Physicians always has extended and will continue to extend a cordial welcome to all members of the County Medical Society to attend its scientific programs.

A special meeting of the College of Physicians commemorating the Bicentenary of the Birth of Benjamin Rush, a distinguished physician before, during and after the period of the American Revolution and one of the Founders of the College of Physicians, was held on the evening of November 5, 1946. The program in honor of the memory of Dr. Rush consisted of two important communications under the auspices of (a) the Benjamin Musser Lecture III and (b) the Thomas Dent Mütter Lecture LIX, both endowed lectureships of the College of Physicians. The former lecture entitled "Benjamin Rush from the Perspective of the Twentieth Century," was delivered by Richard H. Shryock, Ph.D., Professor of History, University of Pennsylvania; the latter, entitled "Benjamin Rush's Theories on Blood Letting after 150 Years," by O. H. Perry Pepper, M.D., Professor of Medicine, University of Pennsylvania. Both presentations[1] were very interesting and highly informative and were well received by a large, attentive and interested audience.

The College of Physicians awarded the Alvarenga Prize on July 14, 1946 to William H. Feldman, D.V.M., M.S., Professor of Comparative Pathology, Mayo Foundation for Medical Education and Research, in recognition of his important work on chemotherapy of tuberculosis. On the evening of October 2, Dr. Feldman delivered the Alvarenga Prize Lecture VI to a large audience in Mitchell Hall of the College of Physicians on the subject "The Newer Chemotherapy of Tuberculosis."[2]

Under the auspices of the Weir Mitchell Fund and through the generosity and cooperation of a large number of Non-Veteran Fellows, the College of Physicians on the evening of October 30, 1946 was enabled to give a dinner in honor of the Fellows of the College who are Veterans of World War II. Of the 127 Resident Veteran Fellows and 12 Non-Resident Veteran Fellows, 85 were present at the dinner. The hosts at the dinner were nearly 200 Non-Veteran Fellows.

It was a great pleasure to greet so many Fellows who recently returned from war service and to welcome them back into active participation in the activities and functions of the College. The good spirit and fellowship manifested at the dinner was acclaimed by all present. Your President would be remiss did he not at this time and place express appreciation to the Fellows of the College for their wholehearted participation in this social affair. The Entertainment Committee, especially, is to be commended for its excellent direction in planning and conducting this Weir Mitchell Dinner.

Attention is directed to the reports of the Officers, Committees, and Sections of the College, now available to the Fellows for reading in the office of the College. The annual report on the library should be read by every Fellow. Mr. McDaniel, the Librarian, has prepared an excellent and detailed account. The Fellows of the College are indebted to him for reporting to the extent that he has on our renowned and acclaimed library. The report of the Librarian, together with the annual reports of the Committee on the Mütter Museum; the Committee on College Collections; and the annual report of the Publication Committee and the Transactions of the Sections of the College will be printed in *The Transactions and Studies of the College* along with the President's address. All of these reports merit careful reading.

With the conclusion of this Business Meeting Dr. J. Harold Austin retires as Secretary of the College of Physicians after serving in this capacity continuously for a period of ten years. He has filled this important position with distinction and honor. The entire Fellowship of the College is greatly indebted to him for his faithful and highly efficient service.

[1] Printed in the *Transactions & Studies*, December, 1946.

[2] Printed in the *Transactions & Studies*, December, 1946.

# Annual Report on the Library*

IN OUR report for last year, we reviewed the immediate effects of the war on the library, as regards both material received and the use of the library. Writing in December, 1945, we felt justified in displaying considerable optimism over the future. In order to indicate whether or not this optimism is renewable at this time, we have, in the statistical part of our report below, contrasted the 1946 and 1945 figures with those for 1939 wherever the contrast was thought to have any indicative value. A conservative optimism is, we believe, still in order. Very considerable amounts of the foreign material duly arrived. For the earlier years of the war, the files are remarkably complete; losses are chiefly noted (as might be expected) in the files for the years 1944 and 1945. So undetermined still is the damage to publishers' stocks from bombing and other causes; so uncertain the knowledge of what issues were actually published, that it will take considerable time yet before the full picture is recognizable. Meanwhile, we have the assurance that every effort will be made to reproduce in some form or other issues whose stock was totally lost or preserved in insufficient quantities.

As for the use of the library, it may readily be seen that the anticipated steady rate of recovery was easily maintained.

While optimism is clearly justified in these areas of our domain, there are disquieting features about which it would be well for the Fellows at large to be informed.

## Legends

### I

Old legends die a very lingering death. One of them that still occasionally arises to plague us is that the library is a sacrosanct possession of the College to which access is still practically unobtainable except for the Fellows of the College. Of course, the truth is quite to the contrary. Any one in the world is free to read in the library, with no questions asked. There is, furthermore, no restriction whatever on the number of persons to whom an individual Fellow may extend the privilege of withdrawing books. In the pas decade or so, we have taken every means tha offered to make it known that the resources of th library were at the disposal of any one wishing t make legitimate use of them. And yet this legen still occasionally crops up, even in the conversatio or questions of the Fellows themselves.

### II

An even more disturbing legend, from the practica standpoint, is that which holds that the Colleg and the library are so well-endowed that neithe mother nor daughter is subject to that commo ailment—financial troubles. The presidents of th College have, in their annual addresses, steadil sought to combat the crippling effect of this legend But it still in unholy measure persists.

In our annual report printed in vol. 8 (1940-41 of the *Transactions & Studies* we described at som length the financial structure of the library. W showed that the library received about two third of its support from endowed funds left in it interest, about one third in annual appropriation from the College. Barring additional endow ments, the library can never be maintaine adequately without annual appropriations fror the College.

Since those far-off days of 1940-41, much ha happened to effect the financial fortunes of th College and the library. From the year of ou entrance into the war, the College's incom naturally declined, and it was unable to make it customary annual appropriation to the library Cut off from receipt of—and of course paymer for—all foreign material except the British, th library nevertheless had in mind the possibility hopeless though it often seemed, that the end c the war would find it in a favored position a regards access to the wartime foreign material. I put aside what it could against this eventuality- what it could, note, not what it would normall have allotted to this purpose, because in th meantime all costs (notably those of binding) wer advancing and the raising of our pitiful salar levels (because of the manpower situation) becam not an act of virtue or justice but an act of absolu necessity.

* November 1, 1945–October 31, 1946.

The past year brought to an end one of our ıncertainties, only to breed others. The amount ›f wartime foreign material collected and saved for ıs ranged far beyond our most optimistic hopes. The loss of the College's aid in the war years, on he other hand, and the still increasing costs of all naterial—human and non-human—required for he proper functioning of the library created a erious financial problem not yet solved and olvable only by the informed aid of Fellows of the College and others who know what the library neans to medical practitioners and research men nd institutions in this area.

III

Another of our ill-fated and mischievous legends s to the effect that the library ranks in importance ext to the Army Medical Library, in Washington. Being human, we are often temped to think so urselves when a question leads us to some articularly rare periodical or book or pamphlet tanding modestly in our stacks; when some noted oreign writing physician is moved to say that he ever had the pleasure of working in such a brary in Vienna, or Berlin, or Prague; when equests for loans come from all over our country, ven, sometimes, from Washington. But we do ot succumb to the temptation, because we know etter. Our library does not rank in importance ext to the Army Medical Library, and it would be riminal if it did. Equidistant—and a short istance at that—from the Washington library nd the magnificent library of the New York cademy of Medicine, its location in one of the ıajor medical centers of the country asks for it a ıajor research status, assuredly, but one in no ense in competition with the library to the north, erving a much larger population, and the library o the south, properly designated as the National Iedical Library.

Facts

egends do, sometimes, have their origin in fact nd not in fancy. It may well be that in earlier ays access to this library was difficult, if not npossible, for those not Fellows of the College; ıat the College and its library were able to afford ıe serenity derived from economic sufficiency; ıat the library ranked next in importance to the rmy Medical Library (formerly the library of the urgeon-General). But these legends today have st whatever validity they once had; we would do well to return them to Valhalla and face the facts of our own time.

The opening of the library to the medical profession and its ancillary sciences at large has created an entirely new set of administrative problems, though some of these would have arisen in any case, as a result of the increasing dependence of clinical medicine upon so-called pre-clinical medicine. Collections that were adequate in their scope twenty-five years ago are today inadequate for the daily needs of a major medical research center. An untrained, or Topsy-trained, staff can no longer service satisfactorily the highly technical, complex material which a library serving such a center must have, if it is properly to fulfil its functions.

As we have indicated above, the geographic situation of our library and the remarkable development of inter-library coöperation in recent years remove any necessity of striving to cover fully the vast ramifications of the literature of the medical sciences today. But any library which wishes and is expected to supply and adequately service even the basic literature required by the research, teaching, and practicing activities of some three thousand physicians, five medical schools, 70-odd hospitals, five medical publishing houses, and (not least) the pharmaceutical houses in the area has, still, a considerable job on its hands. And this twentieth-century job the library is now attempting to do on a nineteenth-century economic foundation.

It is perhaps now clear how disadvantageous legends can become when they outlive the truth that gave rise to them. The library badly needs to be seen today from a new perspective. It is still a great medical library, but its future course is uncertain. Shall it stumble along, clothed in the pride of ignorance, becoming less and less great, less and less useful as its endowments become more and more inadequate? Or shall its new status as one of the greatest assets the medical community and the community-at-large has be promptly recognized and the challenge courageously met? We can but set forth the facts and pose the question. The answer must come from the library's friends and dependents—the physicians, the medical schools, the hospitals, the medical publishing and industrial houses, of the City of Philadelphia. We look back over the years to 1789, the year of the library's founding, and see

that it has come far indeed. But there is need now for the same quality of honest, pioneer vision shown by the College's founding fathers.

### The Past Year

The return to a research use of the library is perhaps best demonstrated in the figures representing the number of volumes consulted in the library. While the figure for the year under review by no means equals that for the year 1939, the increase over the preceding year is substantial enough to indicate that the library is well on the way to full resumption of its most important function. The inter-library loan and photostat figures, in turn, representing services offered freely by the library only in recent years, are eloquent testimony to the considerable extra-territorial use of the library.

It is gratifying to be able to report that the Smith, Kline & French laboratories again signalized their appreciation of the library's services by a grant of $1,000. This example of enlightened self-interest, if generally followed by the many other organizations and institutions benefiting from the library's services, might well institute a new era of coöperative support of a library which gives so much to the community.

From Dr J. L. T. Appleton, dean of the School of Dentistry of the University of Pennsylvania, the library received a much appreciated gift of $100, donated as a spontaneous and very generous recognition of the assistance accorded the donor by the library over a number of years.

Though in recent years it has not been possible to add by purchase very materially to our historical collections (much used though they be), we still have, fortunately, a number of Fellows and other friends who have these collections at heart and slip us a nugget from time to time. Among them we must single out, for their more frequent thoughtful gifts, Drs Burton Chance, E. B. Krumbhaar, G. N. J. Sommer, and William Pepper. The late Dr Joseph Walsh (who bequeathed his collection to the library) was another such friend. Gifted with a keen historical sense, he preserved much of the contemporary documentation on the early history of tuberculosis in Pennsylvania. The student of this subject will rejoice indeed to find this material and the superb Lawrence Flick collection housed in the same library. Dr Walsh was also, as many know, an authority on Galen, and our library is now the richer by many a rare Galen edition and hard-to-come-by study of his works. Another important collection (which will receive more detailed attention at a later time) was presented to the library by Mr Joseph Leidy, through the influence of our Fellow Dr George D. Gammon: a collection of manuscript material left by the donor's namesake, the great Dr Joseph Leidy. Still another collection, impressive in quantity and even more so in quality, was received through the farsightedness of our Fellows Dr Clifford B. Farr and Dr Earl D. Bond. This consisted of the entire historical section of the library of the Pennsylvania Hospital's Department for Mental and Nervous Diseases. Especially rich in early reports of mental institutions and in early American and foreign psychiatric journals and books, this collection makes a notable addition to our holdings in this field. From the libraries of the late Dr. E. B. Hodge (at his death, vice-president of the College) and Dr. Arthur Newlin, we were able to obtain various useful items, through the kindness of Drs. C. A. Hatfield and John H. Arnett (member of our Library Committee), respectively. Dr. William N. Bradley continued his alert care of the Bradley Collection of photographs of Philadelphia physicians portrayed in the several art forms, making a number of important additions. Dr. Samuel B. Sturgis' serious illness through a great part of the year held up his work on the Department of Medical Art, and explains the absence of an annual report from him as an appendix to the library's report. It is gratifying to be able to state that his subsequent complete recovery and retirement from active practice give promise of an interesting report from him next year. This brief paragraph (which does not do justice to a number of kind donors of individual historical items) makes it clear, we hope, that, though the library was unable itself, for lack of funds, to make any notable additions to the historical collections, very important additions were nevertheless made through the thoughtful kindness of our friends.

Our historical collections made possible three major exhibits during the year that were evidently rewarding to our visitors. In an exhibit commemorating the Roentgen anniversaries we had the inestimable assistance of our Fellows Drs George E. Pfahler, William S. Newcomet, and Thomas S. Stewart, pioneer Philadelphia roentgenologist

who graciously loaned examples of the earliest roentgen apparatus. As is indicated in the report of the Committee on College Collections, the College was subsequently exceedingly fortunate in having these instruments donated or promised to it. The Benjamin Rush and Ether anniversaries were also commemorated by exhibits of rarities that could only be produced by a library that had assiduously sought out and preserved the documents essential to the study of the history of medicine.

Under the will of Sir William Osler, among the curators of his library at McGill University is the chairman of the Library Committee of this College, Osler thus commemorating in perpetuity an affection for this library that stemmed from his Philadelphia days. Few of our chairmen have found it possible to attend the annual meetings of the curators in Montreal. It deserves recording, therefore, that our present chairman, Dr. Chance, during his incumbency, has faithfully fortified the strong bond of sentiment existing between these two great libraries by annually attending the meetings of the curators of the Osler Library.

*The Staff.* Casualties here continued heavy. Our popular Mrs. Shaffer, assistant in charge of the Reading Room, and Mrs. Mary Bliss, photostat operator and page, retired to domestic life; our assistant cataloguer, Miss Gwen MacMurray, yielded to the overtures of the Great God Mammon. Of the remaining staff, Miss Clara Manson, our assistant librarian and cataloguer, Mrs. Elizabeth Bready, assistant in charge of the current periodicals room, Miss Kathryn Haegele, general assistant and secretary to the librarian, and Miss Anne Ludovici, page and (succeeding Mrs. Bliss) photostat operator, spent a busy and rather trying year plugging up one hole in the dike after another. It is impossible for the librarian adequately to express his appreciation and gratitude to this valiant and talented little band of co-workers.

The librarian continued to serve as editor of the College's *Transactions & Studies* and as secretary of its Hall Committee. In February, 1946, he was appointed an Honorary Consultant to the Army Medical Library and, in October, attended the annual meeting of the consultants in Washington. In March, he was elected president of the Medical Library Association. In connection with the latter, it may be of some interest to the Fellows to know that the meeting that launched the Medical Library Association, in 1898, was held in this city in the office of Dr. George M. Gould, distinguished ophthalmologist, writer, editor, maker of medical dictionaries, and, of course, Fellow of this College. The small founding group was composed of physicians (including Dr. William Osler) and medical librarians (including Mr. Charles Perry Fisher, for 50 years the eminent librarian of this College). So affectionate and intimate was this association between the physicians and their librarians that not until 1933 was a president elected who was not a physician. Today, the Association, becoming increasingly professional as an inevitable result of the rapid growth of medical libraries, provides an honorary vice-presidency reserved for "a physician known for his interest in and aid to the development of medical libraries." Physicians who are not professional medical librarians may still, however, be elected to any office in the Association, and indeed a most active and valued member of the Executive Committee at the present time is Prof. John F. Fulton, of Yale. It is doubtful whether, in the whole complex pattern of professional organization, there is to be found another example of quite such warm and friendly collaboration between 'labor and management'.

The staff as constituted at the time this report is printed is given below. Readers familiar with the library know, however, that stations are filled for relief periods by another member of the staff than the title-holder.

*Assistant Librarian and Cataloguer*

Miss Clara S. Manson

*Assistant in Charge of the Reading Room*

Mrs. Maude G. Maines

*Assistant in Charge of the Periodicals Room*

Mrs. Elizabeth Bready

*Assistant Cataloguer*

Mrs. Mary Elizabeth Grant

*Secretary to the Librarian, and General Assistant*

Miss Kathryn Haegele

*Photostat Operator and Page*

Miss Anne Ludovici

*Page*

Miss Sarah Kologiski

## Inventory

| | 1946 | 1945 |
|---|---|---|
| *Total number of accessioned[1] items* | 165,004 | 163,025 |
| | 1946 | 1945 |
| Incunabula | 415 | 415 |
| Manuscripts (including a few typescripts) | 653 | 638 |
| Other items | 163,936 | 161,972 |
| | 165,004 | 163,025 |
| *Total number of unaccessioned[1] items* | 322,240 | 322,180 |
| Reports | 25,950 | 25,879 |
| Periodicals "reserve"[2] | 5,709 | 5,209 |
| Complete and incomplete volumes of other periodicals not regularly received | 1,575 | 5,133 |
| Theses and Dissertations | 51,499 | 48,582 |
| Pamphlets | 237,507 | 237,377 |
| | 322,240 | 322,180 |
| Total number of current periodical publications regularly received | 1,258 | 899 |
| Portraits[3] | 63,802 | 62,662 |

## Distribution of This Material

| | Accessioned Items | Unaccessioned Items |
|---|---|---|
| General Library (including the Lewis Library) | 160,772 | 322,236 |
| On permanent deposit: | | |
| Gross Library | 3,815 | 4 |
| Parry Library of the Obstetrical Society of Philadelphia | 217 | 0 |
| Mütter Museum[4] | 200 | 0 |
| | 165,004 | 322,240 |

## Current Periodicals

| | Purchased | Exchange or Gratis | Annuals | Totals |
|---|---|---|---|---|
| U. S. A. | 236 | 299 | 12 | 547 |
| Western European Continent | 395 | 17 | 11 | 423 |
| Latin America | 25 | 104 | | 129 |
| United Kingdom and Eire | 80 | 23 | 2 | 105 |
| Canada | 1 | 17 | 1 | 19 |
| Eastern European Continent | 9 | 1 | | 10 |
| Asia | 4 | 5 | | 9 |
| Africa | 1 | 7 | | 8 |
| Pacific Area | 2 | 6 | | 8 |
| Grand Totals, 1946 | 753 | 479 | 26 | 1,258 |
| Grand Totals, 1945 | 415 | 484 | | 899 |
| Grand Totals, 1939 | 688 | 514 | | 1,202 |

[1] Our "accessioned item", or "volume", normally contains not fewer than 100 pages, usually is bound, and always is catalogued. It may comprise a part of a "book" or periodical "volume", one or more complete "books" or periodical "volumes", a collection of reports, pamphlets, or theses. In a few instances, the term applies to miscellaneous items such as a photograph album or a large collection of correspondence or private papers.

The "unaccessioned item" is intended to apply to (usually unbound) pamphlets, reports, theses, or other material of fewer than 100 pages; only a part of this material is catalogued. It should be stressed, however, that in this category are included uncounted thousands of reports and theses of 100 pages or over, as well as smaller classic items, which would quite properly figure in the "number of volumes" claimed by other libraries, and which would indeed figure among our "accessioned items", had our predecessors and we ever been able to accession and catalogue them.

[2] More-or-less complete duplicate volumes of important and much-used periodicals.

[3] Including 114 oil, and 455 other, framed portraits in the care of the Committee on College Collections. The count of portraits represents the number of entries on the cards in the portrait catalogue. The entries represent, in turn, both loose portraits and those in books, many of them, of course, being merely different reproductions of a single original.

[4] The books of the Mütter Museum are not permitted to be removed from the College building.

*Foreign titles:* In January large shipments of material collected and saved for us by our agents on the European continent during the war years began to arrive. In the period covered by this report, 8,480 separate issues of foreign journals for the years 1940–45 were received; of these, 1,311 were Italian for the years 1940–41 only. From these shipments we were able to complete 815 volumes. It is regrettable that rising costs, especially that of binding, prevented us from having more than 195 of the more important of these volumes bound, thus seriously limiting their usefulness. The tidal waves of this material, while more than welcome in the final sense, naturally put our staff under no mean strain. It is a pleasure to report that they dug in on the job with enthusiasm and in record time had this long-awaited material in usable shape.

*New titles:* A total of 48 periodicals were added to the Norris Room in 1945–46. Forty of these were purchased, 8 received in exchange or gratis. There were 34 that began with volume 1.

*Separate Issues* received, checked-in on the cards, and shelved totaled 17,907, including the issues of foreign journals enumerated above. In addition; thousands of duplicate issues were received, as usual, 500 of these were retained for our 'reserve' files, no attempt being made to count those held merely for exchange or other use.

*Visitors* to the Norris Room for the year totaled 4,769.

## Readers' Use of the Library

*Library Hours.* The library adhered to its somewhat curtailed, wartime schedule through March. In April and May, we were on our normal schedule for the academic year: Mondays and Wednesdays, 9:30 to 9:30; other weekdays, 9:30 to 5:30. The summer schedule, effective June 1 through Sept. 15, with minor exceptions noted on our *Booklist*, followed that of recent summers. The library was closed for the period Aug. 5–18, while the Ashhurst and Norris Rooms were being repainted. On Sept. 16, we returned to the schedule prevailing during the academic year. The following legal holidays were observed by the library: Thanksgiving, Christmas, New Year's, Memorial, Independence, and Labor Days.

| | 1946 | 1945 | 1939 |
|---|---|---|---|
| *Number of visitors* | 12,253 | 10,367 | 12,746 |

*Circulation of books:*

| | 1946 | 1945 | 1939 |
|---|---|---|---|
| Number of volumes taken out (Books: 3,139; Periodicals: 4,437) | 7,576 | 6,664 | 8,524 |
| Number of volumes consulted in the library[5] | 36,568 | 30,075 | 49,725 |

*Inter-library loans:* The library sent 986 (1945: 1,099) volumes on inter-library loan to 80 (1945: 67) libraries in 20 (1945: 15) States and has borrowed 13 (1945: 30) volumes from 6 (1945: 15) libraries.

*Photostats:* 3,359 photostatic prints were furnished on request (1945: 2,828).

## Acquisitions and Accessions

Accessioned Acquisitions:

*1946:* 1,979 volumes (1,020 by purchase; 701 by gift; 258 by exchange). (Books: 870; Periodicals: 1,109).

*1945:* 1,285 volumes (775 by purchase; 374 by gift; 136 by exchange). (Books: 612; Periodicals 673).

Non-accessioned Acquisitions:[6]

*1946:* 130 Pamphlets (1945: 1,096).
71 Reports (1945: 60).
2,917 Theses (1945: 661).

### Donations

The individual donors for the past year number 276 (1945: 282). The library is indebted for large gifts of books, pamphlets, and unbound periodicals to the following donors:

Dr. T. C. Barnes; Bibliothèque de l'Université de Copenhagen, Bibliothèque de l'Université de Liége; Biochemical Research Foundation; Biological Abstracts; Boston Medical Library; Drs. B. Chance, K. Chouké, J. M. Deaver; Miss J. Eshner; Drs. C. Farr, A. C. Hatfield (E. B. Hodge Estate), E. B. Krumbhaar; Lea & Febiger; J. B. Lippincott; Josiah Macy,

[5] The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and reference works kept on the shelves in the Reading Room; the Fellows, and occasionally others, by special permission, have access to the book-stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

[6] As usual, not all the pamphlets, theses, and numbers of various journals listed as received had been checked for keeping or discard at the close of the library year.

Jr., Foundation; Dr. J. McLean; Medical Library Exchange; Drs. L. H. Mutschler, J. E. Nathanson; Philadelphia Bibliographical Center; Rockefeller Foundation; W. B. Saunders; Smith, Kline & French; South African Institute for Medical Research; Union Library Catalogue; Universität Bern; Universitäts-bibliotek de Basel; Université de Genève; Université de Lausanne; Université de Paris; Universitets-Biblioteket Lund; Universitets-Biblioteket Uppsala; University of Pennsylvania Library; Drs. J. Walsh (bequest), A. C. Wood; Wyeth, Inc.; Dr. W. Zentmayer.

Various publishing houses have presented volumes as follows: Blakiston Co., 3; F. A. Davis Co., 3; Lea & Febiger, 12; J. B. Lippincott Co., 23; W. B. Saunders Co., 57.

Other individual donors were as follows: Drs. A. Aleson, O. H. Allis, B. J. Alpers, W. S. Bainbridge, F. Beekman, H. Beerman, M. Behrend, N. Blumberg, S. Bradbury, W.N. Bradley; Mrs. A. Brav; Drs. M. S. Briscoe, E. Brown; Prof. L. H. Butterfield; Dr. R. C. Chaffin; Misses Chamberlain; Drs. J. Solis-Cohen, D. L. Cowen, J. W. Croskey, F. X. Dercum, W. A. N. Dorland, J. T. Eads, L. L. Eisenbrandt; Dr. J. H. Arnett (Estate of Arthur Newlin); Drs. H. Freed, H. Friedenwald, J. H. Gibbon, Jr., E. Gibson; Mr. J. E. Gibson; Miss M. Godhold; A. Hunsberger; Drs. C. L. Jackson, R. L. Jenkins, M. Kannerstein, J. V. Klauder, A. Koerner, A. J. Lamberti, F. H. Leavitt; W. R. LeFanu, J. Leidy; Lt. Col. R. Leigh; Drs. B. Masuda, L. H. Mayers; W. B. McDaniel, 2d; Drs. T. H. McGavack, F. Milane, O. W. H. Mitchell; W. H. Ogston; J. Oppenheimer; Drs. F. R. Packard, J. Paton, T. M. Peery, W. Pepper, G. E. Pfahler; Miss A. M. Purington; Dr. S. X. Radbill; Lt. E. A. Rasberry; Dr. J. G. Reinhold; Mr. G. Roberts; Miss S. Roberts; Dr. P. Q. Roche; Prof. A. H. Roffo; Drs. H. C. Ruche, P. J. Sartain (bequest), T. G. Schnabel; Mr. W. C. Shepard; Drs. G. N. J. Sommer, J. M. Swan, J. A. Sweeney, T. T. Thomas, J. M. Thorington, L. Tocantins, J. C. Trent, H. J. Tumen; W. H. H. Turville; Drs. H. Wastl, R. M. Waters, R. M. Watkins; E. Weil; Drs. F. Wittels, I. J. Wolman, F. L. Wood, G. Wood, H. C. Wood, H. McF. Woodbridge; Mrs. S. W. Woodhouse; Dr. DeG. Woodman.

### Exchanges

The *Transactions & Studies* was sent, either as gift or in exchange, to 287 organizations.

The library received large numbers of journals through the Medical Library Association Exchange.

Theses and dissertations to the number of 2,917 have been received on exchange from the following European schools of medicine: Universities of Basel, Bern, Copenhagen, Geneva, Lausanne, Liége, Louvain, Lund, Paris, Uppsala.

### Work of the Cataloguers

| | 1946 | 1945 |
|---|---|---|
| Accessioned items catalogued or recatalogued | 892 | 833 |
| Unaccessioned pamphlets and Fellows' reprints catalogued by author or by author and subject | 965 | 1,530 |

Approved:
Burton Chance
*Chairman*

W. B. McDaniel, 2d
*Librarian*

# Annual Reports of the Committee of the Mütter Museum and College Collections

## The Museum

### *Activities*

The museum was open weekdays from 10–1 and 2–5:15 except Saturday when it was open from 9:30 to 1.

There were 882 visitors during the year.

The fifty-eighth Thomas Dent Mütter Lecture was given by Joseph Stokes, M.D., of Children's Hospital, who spoke on "Studies on Infectious (Epidemic) Hepatitis and Serum Hepatitis." This lecture, originally scheduled for December 1945 was given April 3, 1946.[1]

The fifty-ninth Thomas Dent Mütter Lecture was delivered by O.H. Perry, M.D., Prof. of Medicine, University of Pennsylvania, on November 6, 1946. The title was "Benjamin Rush's Theories on Blood Letting after 150 years".[2]

During the year, a paper, "The History and Growth of the Mütter Museum" by Mrs. Ella N. Wade, curator, appeared in *Transactions and Studies of the College*, April 1946.

Dr. Ralph Pemberton again used specimens from the Museum to illustrate a lecture on lesions of arthritis and ankylosis.

Two anatomy classes from the Dolan College of Embalming visited the Museum with their instructor.

Work was begun on a catalogue of museum specimens, which will eventually be printed in the *Transactions and Studies of the College*.

Mrs. Ella N. Wade was reappointed Curator and Clerk-technician for the year 1945-1946.

### *Accessions*

Presented by Dr. Samuel X. Radbill:

Identification tags, worn on the soldier's person at all times in World War II, on which are recorded dates of Tetanus immunization.

Presented by Dr. G. N. J. Sommer, Trenton, N. J.:

3 angiotribes
1 Emmet's Uterine cutting forceps
1 Outerbridge's knot-tier
1 Mayo vein stripper
1 Knot-tier

Presented by Mayor Bernard Samuel through Dr. Hubley R. Owen:

Machete taken from a Moro Chief of a New Guinea Tribe in World War II.

Presented by Dr. John H. Cloud:

Human ovum showing chorial villi
Skull of a fetus at term

Presented by the estate of Dr. Joseph McFarland:

1 stethoscope
1 pleximeter
1 percussor

## The College Collections

### *Activities*

Oil portraits were cleaned and all framed pictures in the Norris Room were cleaned and rebacked.

Mrs. Ella N. Wade was reappointed Custodian and Clerk-technician for 1945-46.

### *Accessions*

Presented by Dr. Edward F. Corson:

Silver magnifying glass upon which is engraved "The Constant Companion of Dr. Joseph Leidy".

Presented by the estate of Dr. Paul Sartain through Dr. Burton Chance:

Skeleton of an anencephalic fetus
McHardy's London Perimeter

Presented by Dr. Burton Chance:

Vienna Eye Phantom, an operative ophthalmic model

Presented by Dr. J. Monroe Thorington:

Collection of 11 pairs of old spectacles, namely,
3 pairs of ancient Chinese spectacles
1 pair of modern Chinese spectacles
3 pairs of early 19th century spectacles
1 pair of dark spectacles
1 pair of early type Oxford spectacles
1 pair of combination rest and corrective lenses
1 pair of rest glasses used by J. Greenleaf Whittier on his travels

[1] Printed in the *Transactions & Studies*, June, 1946.
[2] Printed in the *Transactions & Studies*, December, 1946.

Presented by Dr. Samuel X. Radbill:

Framed silhouette of John Jones, M.D.

Presented by Dr. William S. Newcomet:

3 early x-ray tubes used during the period from 1896 to 1900

1 induction coil used about 1898

Presented by Dr. Thomas S. Stewart:

5 early x-ray tubes used from 1896 to 1902

1 induction coil (1899) used by Dr. Charles Lester Leonard

Presented by Dr. William N. Bradley:

Key to the bedroom of Dr. S. Weir Mitchell

Tube for administering ethyl chloride for local and general anesthesia.

Presented by Dr. Edward B. Krumbhaar:

Two blood donor's buttons, one bronze and one silver.

Presented by Mr. Orville H. Bullitt:

Gold-headed cane formerly belonging to Dr. Samuel D. Gross

Presented by his granddaughter Mrs. Charles Biddle:

Medicine chest formerly belonging to Mr. John Correy (1784–1845) which he carried on many voyages.

Presented by Mrs. Frances R. Brooks, of Cape May, N. J.:

Oil portrait of Dr. Philip Syng Physick by R. F. Reynolds in 1860, after Inman.

Presented by Mrs. Edward B. Krumbhaar:

Oil portrait of Dr. Edward B. Krumbhaar by Daniel Garber, 1945.

Presented by Col. William Innes Forbes:

Two small instrument cases

Presented by Dr. B. B. Vincent Lyon:

Illuminated cabinet containing 100 lantern slides reviewing "The Story of Biliary Tract Drainage".

Presented by Dr. Henry Pleasants of West Chester, Pa., who received it from Dr. Horner's granddaughter, Regina Horner:

Microscope and accessory equipment with specimen slides used by Prof. William E. Horner of the University of Pennsylvania circa 1825.

Oscar V. Batson,
*Chairman*

# Annual Report of the Publication Committee

This report covers the four numbers of the *Transactions & Studies* published within the College's fiscal year ending November 30, 1946: namely, v. 13, nos. 3 and 4, and v. 14, nos. 1 and 2.

The total number of pages printed was 162, 28 fewer than in the preceding four numbers.

Of the eight lectures sponsored jointly by the College and the Philadelphia County Medical Society, which form the indispensable nucleus of the scientific material theoretically available to us, two were not available for publication: Dr. T. Duckett Jones' lecture in November, 1945 (arranged for by the County Society); and the College's Newbold Lecture by Dr. John Alexander, in December, 1945.

Two developments of importance to the future course of the *Transactions & Studies* occurred during the year. One, discernible in the contents of the numbers under review, was the magnificent coöperation of the clerk of the Section on General Medicine in obtaining for the *T & S* not only abstracts of the shorter presentations before the Section but the full papers read by a number of distinguished guest speakers. The papers of Dr. John S. Lawrence, Prof. W. U. Gardner, and Dr. Robert A. Moore, obtained from this source, may be cited as indicating how much poorer in quality these numbers would have been without Dr. Leandro M. Tocantins' valuable coöperation. Further, one of the abstracts he provided (of Dr. F. Maurice McPhedran's paper on combined injection of vitamins and vaccines) appeared to be of such interest to the field of medical research that it was decided to place it among the main articles. There is no reason on earth why the Section on General Medicine, under its new policy of presenting programs comprised of shorter papers, of local origin, and full presentations by guest speakers, should not contribute materially to the scientific coffers of the *T & S;* and there is reason to hope that the practice begun by Dr. Tocantins will be carried on by his successors.

The second hopeful (though not active within the period covered) development is the decision by both the College and the County Society to require that the monthly lectures be made available for publication. This should assure us the minimum of scientific material needed to maintain interest in the journal.

As could only be expected, the supply of historical studies remained low; and yet we were able to hang onto our titular franchise. Prof. Kitchel's study of an unpublished notebook of medical lore gathered by George Eliot for her *Middlemarch* must have interested anyone familiar with that famous medicated novel. By coincidence, Mr. James E. Gibson's "Benjamin Rush terminates a post-war mutiny" appeared at exactly the time a similar incident among our armed forces was receiving much attention in the press. One of the local papers did a feature story on the article, which was also picked up by one of the press associations. Mrs. Wade contributed a history of the Mütter Museum, and our Fellow Dr. Samuel X. Radbill, a brief study of interest to pediatrists and others interested in the early medical history of our country.

In connection with the financial summary which follows, it is proper to recall the decrease in number of printed pages and a substantial increase in printing costs.

### Financial Summary

*Receipts*

| | | |
|---|---|---|
| Appropriation | $900.00 | |
| Income from publication funds | 678.42 | |
| Sales and reprints | 80.27 | $1,658.69 |

*Expenditures*

| | | |
|---|---|---|
| Printing, mailing, and reprints | $1,466.84 | |
| Stenciling envelopes | 15.60 | |
| Miscellaneous | 28.09 | 1,510.53 |
| *Balance* | | $148.16 |

W. B. McDaniel, 2d
*Editor*

Approved:

John Porter Scott
*Chairman*

# Annual Reports of the Sections

## General Medicine

The membership of the Section increased during the year from 127 to 144.

Seven meetings of the Section were held, one jointly with the Philadelphia Urological Society. The average attendance was about 200. At five of the meetings there were non-resident guest speakers; at all of the meetings except the one held jointly with the Philadelphia Urological Society presentations were made by members of the Section and local guests.

William G. Leaman, Jr.
*Clerk*

## Medical History

The Section on Medical History remained inactive, but it is expected that its meetings will be resumed in the coming year.

William G. Leaman, Jr.
*Clerk*

## Ophthalmology

The total membership of the Section is now 58. Of this number, 53 have paid dues; one member was excused from payment because of his membership in the Armed Forces and the dues of one member remain to be paid, as do those of three new members.

The meeting held in January was a joint one with the Philadelphia Roentgen Ray Society.

The Ninth Annual de Schweinitz Lecture was delivered by Algernon B. Reese, M.D., of New York, on November 21st.

The Zentmayer Prize was awarded to Harold G. Scheie, M.D., and Norman E. Freeman, M.D., for their paper, "Angioid Streaks of the Retina Associated with Peripheral Vascular Disease", presented on March 21st.

George F. J. Kelly
*Clerk*

## Otolaryngology

During the last year there have been seven meetings held at the College, in coöperation with the Philadelphia Laryngological Society, the two societies conducting alternate meetings. The Section arranged for and conducted the December (1945), February, April, and October meetings, at which the average attendance was 48. The total membership is 55.

Oscar V. Batson
*Clerk*

## Public Health, Preventive and Industrial Medicine

The Section had 36 paid memberships for the year 1936.

There were two meetings held during the past year. The first meeting was on March 26, 1946. At this meeting, the Section as a whole was entertained by the General Motors Acceptance Corporation at a dinner at the Warwick Hotel. Following dinner, the Section was entertained with a moving picture entitled "The Doctor in Industry". The attendance at this meeting was fairly good, and we were indebted to the General Motors Acceptance Corporation for a very enjoyable and instructive evening.

The second meeting was held at the College on November 5, 1946. The subject for this meeting was Venereal Disease Control, and papers were given on various aspects of this subject by Dr. E. C. Drescher, Dr. Norman Ingraham and Dr. Howard P. Steiger.

David A. Cooper
*Clerk*

# Transactions of the Sections

## SECTION ON GENERAL MEDICINE

*October 28, 1946*

CHANGES IN BLOOD AND BODY FLUIDS IN PROLONGED FASTING. F. William Sunderman, M.D. (Commentator: Russell S. Boles, M.D.) (*Abstract 1, below.*)

CONGENITAL HEMOLYTIC ICTERUS: REPORT OF A CASE ASSOCIATD WITH SEVERE COLITIS CURED BY SPLENECTOMY. C. S. Stahlnecker, M.D. (Commentator: Lowell Erf, M.D.) (*Abstract 2, below.*)

RECENT EXPERIMENTS ON THE GENESIS AND CONTROL OF LEUKEMIA. Jacob Furth*, M.D. (*Abstract 3, below.*)

*November 25, 1946*

THE USE OF A LOW SALT NEUTRAL-ASH DIET IN THE TREATMENT OF CONGESTIVE HEART FAILURE WITH EDEMA. E. A. Daugherty*, M.D. (Commentator: Thomas M. Durant, M.D.) (*Abstract 4, below.*)

THE TYPE AND LOCATION OF MYOCARDIAL INFARCTS AND THEIR RELATION TO THE ELECTROCARDIOGRAM. John J. Sayen*, M.D., and Warner F. Sheldon*, M.D. (Commentator: Francis C. Wood, M.D.)(*Abstract 5, below.*)

AN EVALUATION OF THE USE OF ANTICOAGULANT THERAPY IN CARDIO-VASCULAR DISEASES. Irving S. Wright*, M.D. (To be published in the *Transactions & Studies*, April, 1947.)

## SECTION ON OPHTHALMOLOGY

*October 24, 1946*[1]

ADENO-CARCINOMA OF THE LACRIMAL GLAND FOLLOWING A MIXED TUMOR OF THIRTY YEARS' DURATION. I. Edward Rubin*, M.D. (Commentators: Jacob Vastine, M.D., Robert Groff, M.D., Edmund B. Spaeth, M.D.)

PRESENTATION OF CASE OF CORNEOSCLERAL INVOLVEMENT WITH PERIARTERITIS NODOSA. (Lantern slide demonstration.) Frederick Herbert*, Capt., MC, USN.

HYDRATION PROPERTIES OF EXCISED CORNEA AND FACTORS RESPONSIBLE FOR TRANSPARENCY. William M. Hart*, PH.D. (Commentator: Francis H. Adler, M.D.)

*November 21, 1946*

PIGMENTED TUMORS. Algernon B. Reese*, M.D. (Ninth Annual de Schweinitz Lecture.)

*December 19, 1946*

EXPERIMENTAL INVESTIGATION OF THE PATHOGENICITY OF DIPHTHEROIDS ISOLATED FROM HUMAN CONJUNCTIVA. Charles Weiss*, M.D.

THOUGHTS DERIVED FROM AN EXPERIENCE IN TESTING THE COLOR VISION OF THOSE WITH DEFECTIVE COLOR SENSE. Burton Chance, M.D.

## SECTION ON OTOLARYNGOLOGY[2]

*October 16, 1946*[3]

EVOLUTION OF AMERICAN OTOLARYNGOLOGY TOWARD A FUNCTIONAL BASIS. William Gordon, M.D. (Commentator: Walter Roberts, M.D.)

THE THYRO-GLOSSAL DUCT.

THE NORMAL DUCT. Oscar V. Batson, M.D.

SURGICAL REMOVAL OF A CYST (motion picture). William A. Lell, M.D.

A CASE OF LIPOID PNEUMONIA WITH RECOVERY. William A. Lell, M.D.

*December 18, 1946*[3]

AMYLOIDOSIS OF THE LARYNX: Report of a Case. J. P. Atkins, M.D.

A NEW DRUG FOR THE CONTROL OF COUGH. Louis E. Silcox, M.D.

STREPTOMYCIN THERAPY. Philip A. Marden*, M.D.

## SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

*March 26, 1946*

"The Doctor in Industry" (motion picture). Dinner meeting, as guests of the General Motors Acceptance Corporation.

* By invitation.

[1] The presentations at this Section are customarily abstracted in the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

* By invitation.

[2] The presentations at this Section are customarily abstracted in the *Archives of Otolaryngology*.

[3] Joint meeting with the Philadelphia Laryngological Society.

*November 5, 1946*

SYMPOSIUM ON THE PUBLIC HEALTH ASPECTS OF VENEREAL DISEASE

NATIONAL OUTLOOK FOR VENEREAL DISEASE CONTROL. Erwin C. Drescher*, M.D., Surgeon, U. S. Public Health Service.

PHILADELPHIA'S SHARE IN VENEREAL DISEASE CONTROL. Norman Ingraham, Jr.*, M.D.

A PRACTICAL OUTLINE OF MODERN VENEREAL DISEASE TREATMENT. Howard P. Steiger*, P. A. Surgeon, U. S. Public Health Service.

## ABSTRACTS

### *Abstract 1*

CHANGES IN BLOOD AND BODY FLUIDS IN PROLONGED FASTING. F. William Sunderman, M.D.

Studies are reported on the changes that occurred in the blood and body fluids of a severely, emaciated individual who had undergone a rigorous, voluntary fast for an alleged period of 45 days.

It has been shown that in fasting, when the body is deprived of salt, the chloride concentration may be decreased to a much greater extent than the total base concentration. Moreover, the chloride concentration may be compensated almost entirely by the substitution of bicarbonate derived from endogenous sources. These findings direct attention to the mobility and secondary position of chloride and bicarbonate in the electrolyte pattern of serum. The factors regulating the serum electrolytes appear to be more directly concerned with the maintenance of a constancy in the cation concentration than with the distribution of the individual anions. In prolonged fasting, serum bicarbonate may replace serum chloride without any apparent detriment to the organism.

The following additional changes in the composition of the serum were observed at the end of the fasting period:

The concentrations of serum magnesium and calcium were increased.

The concentration of serum protein was within normal range of values, although the ratio of albumin to globulin was increased to 4.2.

The concentration of total cholesterol was essentially normal, however, the esterified portion was greatly increased and represented about 95 percent of the total cholesterol.

The concentrations of serum urea nitrogen, uric acid, and creatinine were all increased above their post-fasting levels.

No gonadotrophins were detected in the urine at the end of the fasting period.

The serum volume and the extracellular fluid volume were both elevated in relation to the fasted weight, but were essentially within the normal range of values when calculated in relation to the normal weight. The data suggests that the circulatory bed had not been greatly altered by fasting.

Within six weeks after discontinuing the fast, the subject had gained his normal weight and the concentrations of the various serum components that had been measured, were within the normal range of values.

* By invitation.

### *Abstract 2*

CONGENITAL HEMOLYTIC ICTERUS: REPORT OF A CASE ASSSOCIATED WITH SEVERE COLITIS CURED BY SPLENECTOMY. C. S. Stahlnecker, M.D.

The following case of congenital hemolytic icterus is presented to emphasize some of the difficulties that may be encountered in diagnosis and because of the unusual association with a severe colitis.

J. M., a thirty year old woman, was admitted to the hospital with a complaint of shortness of breath of two weeks duration. She stated that she had been anemic since childhood and had had irregular treatment with liver and iron at ages 18, 22 and 26. Physical examination was normal except for marked pallor and a loud systolic murmur heard all over the precordium. Her red blood count was 1,200,000 with 4.3 grams of hemoglobin. There was a reticulocytosis of 42%. The red cell volume index was 1.4. The color index was 1.1. A red cell fragility test was normal and the blood smear was reported as compatible with pernicious anemia. X-ray studies of the gastrointestinal tract revealed no abnormalities. A gastric analysis showed the presence of free hydrochloric acid. After two weeks the patient left the hospital against advice. She was signed out as anemia, type undetermined. Three weeks later the patient was readmitted. She had developed a severe watery diarrhea. Her red blood count had falled to 670,000 with 20% hemoglobin. A high reticulocytosis persisted. Red cell fragility tests were repeated and showed a

markedly increased fragility. Hemolysis began at 0.64% and was complete at 0.40% (control, 0.40 to 0.28). She ran an irregularly febrile course with elevations to 104 degrees F. The profuse diarrhea failed to respond to a variety of medication. She averaged fifteen stools daily, many of them grossly bloody. No splenomegaly could be detected by physical examination or x-ray. Repeated transfusions caused only a transient improvement in the red blood count.

On the thirty-fifth hospital day splenectomy was performed. Her spleen was enlarged. It weighed 400 grams. The colon was grossly thickened and injected throughout.

Her postoperative recovery was complete. No further transfusions were required. The diarrhea slowly subsided. She is now well and active, six months after operation. Her red cell fragility remains increased at approximately preoperative figures.

It is felt that this patient's severe colitis was an unusual complication of a hemolytic crisis. We delayed operaion while attempting to combat her colitis, but now feel that this complication is an even more pressing indication for immediate splenectomy in this disease.

*Abstract 3*

Recent Experiments on the Genesis and Control of Leukemia. Jacob Furth[4], M.D.

A review of the basic findings of experimental leukemia which have been amply confirmed introduces this paper: Leukemia is a neoplasm of hemopoietic cells. The manifestations of the disease (as blood involvement, localization of leukemic infiltrations, duration of illness etc.) depend not on the host but on the character of the malignant blood cell. Lymphosarcoma and leukemia are extreme forms of the same disease. Human leukemia is essentially the same as leukemia of other mammals. The immature cells of leukemoid infiltrations do not possess neoplastic characteristics, that is unrestrained growth as indicated by transplantability.

The causes of leukemia are genetical and environmental. The genetic factors have been established in well controlled experiments with inbred strains of mice. The mode of inheritance varies greatly with different inbred high and low leukemia strains. There are maternal and nursing factors. The proven extrinsic leukemogenic agents include x-rays, carcinogenic hydrocarbons and benzol. One agent may enhance the leukemogenic ability of another agent (coleukemogenesis). Underfeeding decreases the incidence of leukemia in mice and retards the malignant transformation of normal blood cell precursors. In an inbred strain of mice in which leukemia is often associated with thymic lymphoma removal of the thymus will prevent leukemia and increase the life span.

The number of agents which prolong the life of leukemic animals is increasing; they include x-rays, radioactive isotopes, neutrons, arsenicals, benzol, Compound E of adrenal cortex, certain carcinogenic hydrocarbons etc. These agents can serve as a nucleus for further chemotherapeutic studies. No compound is yet available which would control all types of leukemia. It is desirable to work out methods which would indicate which agent is most effective in a given case.

The presentation closes with a discussion of the modern concepts of leukemia and neoplasia and with the expression of the hope that a wider use will be made of leukemic animals, now available in large numbers, in further attempts to control this disease.

[4] Professor of Pathology, Cornell University Medical School.

*Abstract 4*

The Use of a Low Salt Neutral-Ash Diet in the Treatment of Congestive Heart Failure with Edema. E. A. Daugherty.

A clinical study of 75 patients suffering from congestive heart failure with edema, treated with a neutral-ash low sodium (1.0 gms. or less) diet, with an unlimited fluid intake, was presented.

The results indicate that in the presence of a low salt neutral-ash diet, water is a valuable diuretic and need not be restricted. Restriction of water only adds to the discomfort of the patient, and may produce serious cellular dehydration.

In the presence of congestive heart failure, edema develops because the kidneys are unable to excrete sodium, and water is retained in an attempt to maintain a normal electrolyte balance in the extracellular edema fluid.

In the presence of a low salt neutral-ash diet, the alkaline sodium salts of the edema fluid are mobilized and with an adequate fluid intake, the kidneys are able to excrete sodium chloride and water, and a spontaneous diuresis ensues.

Mercurial diuretics are indicated for severe respiratory distress resulting from the mechanical

embarrassment of excessive edema fluid. The number and frequency of injections are reduced with a low salt diet, and with an adequate fluid intake the dangers of post-diuretic dehydration are minimized.

The degree of activity and comfort enjoyed by ambulatory patients maintained on a low salt diet with adequate fluid intake has been much greater than was our experience with a restricted fluid regime.

*Abstract 5*

THE TYPE AND LOCATION OF MYOCARDIAL INFARCTS AND THEIR RELATION TO THE ELECTROCARDIOGRAM. John J. Sayen, M.D., and Warner F. Sheldon, M.D.

The purpose of this report was to show how the tridimensional position of lesions in the myocardium could be found and illustrated, and then to demonstrate certain relationships between the position of acute infarctions and the electrocardiographic patterns recorded shortly before death.

*Description of technique:* (1) For localization and study of lesions ten serial sections were made of the ventricles in planes transverse to the long axis of the heart. Such sections were composed of a heavy circular mass of muscle made up of the left ventricular walls and the equally thick septum, and a thinner crescentic right ventricle attached to one side of the main mass. Characteristics of the majority of infarcts and scars in the ventricles were as follows: (a) they had a tendency to be confined to planes in the wall, especially the inner half or the middle portion, the whole wall being involved only in massive lesions and the outer portion rarely involved alone; (b) lesions were confined largely to the left ventricle and the septum and their pattern in the latter tended to continue that in the left ventricular walls. Right ventricular lesions were rare, except for minor extensions of lesions predominantly in the left ventricle. The septum pathologically was best considered as if it were a part of the left ventricle.

(2) Because of these relationships it proved practical to illustrate lesions by reconstructing them as they would have appeared after longitudinal trisection of the conical left ventricular-septal muscle mass along its midlateral wall and the anterior and posterior interventricular grooves (the right ventricular walls having first been cut away). By drawings of the inner aspect of the three resulting sections—the anterolateral and posterolateral left ventricular wall and the septum—the location of lesions and their position in depth could be illustrated for reference and comparison.

*Electrocardiographic correlation*: The electrocardiograms and drawings of the infarcts of five cases were then presented to show (1) the diagnostic patterns associated with massive anterior and posteroseptal lesions and (2) the abnormal but non-specific patterns, characterized especially by RS-T segment depression, associated with acute lateral, posterolateral and midseptal infarcts, and also posteroseptal infarcts confined to the inner portion of the left ventricular wall. It was emphasized that in the series studied so far the frequency of lesions of type (2) was not much less than that of type (1).

# List of the College Lectures, 1946*

*January 9, 1946*

Hundley, J. Mason, Jr. Urinary Tract Pathology Engendered by Changes in the Generative System. (*Transactions & Studies*, April, 1946.)

*February 6, 1946*

Eagle, Harry. Recent Studies in Arsenical Chemotherapy (*Nathan Lewis Hatfield Lecture XXX*). (*Transactions & Studies*, June, 1946.)

*March 13, 1946*

Friedell, Hymer L. Atomic Energy and Cancer. (*Transactions & Studies*, June, 1946.)

*April 3, 1946*

Stokes, Joseph, Jr. Studies on Infectious (Epidemic) Hepatitis and Serum Hepatitis. (*Thomas Dent Mütter Lecture LVIII*). (*Transactions & Studies*, June, 1946.)

*September 18, 1946*

Pendergrass, Eugene P. The Atomic Bomb Experiments in the Pacific, with a Consideration of the Relationship of Atomic Energy to the Future of Medicine. (*Transactions & Studies*, December, 1946.)

*October 2, 1946*

Feldman, William H. Studies in Chemotherapy of Tuberculosis, including Use of Streptomycin. (*Alvarenga Prize Lecture VI*). (*Transactions & Studies*, December, 1946.)

*November 6, 1946*

(Special meeting commemorating the bicentenary of the birth of Benjamin Rush)

Shryock, Richard H. Benjamin Rush from the Perspective of the Twentieth Century (*Benjamin Musser Lecture III*). (*Transactions & Studies*, December, 1946.)

Pepper, O. H. P. Benjamin Rush's Theories on Blood Letting after 150 Years (*Thomas Dent Mütter Lecture LIX*). (*Transactions & Studies*, December, 1946.)

*November 13, 1946*

Abernethy, Theodore J. Experiences with Primary Atypical Pneumonia in World War II. (*Transactions & Studies*, December, 1946.)

*December 4, 1946*

Dingle, John H. Experimental Studies of the 'Common Cold' in Human Volunteers (*James M. Anders Lecture XXI*).

* Held jointly with the Philadelphia County Medical Society, except for the Special Meeting on November 6. The February, April, October, and December lectures were arranged for by and delivered at the College; the other scientific lectures were arranged for by the County Society and were delivered in its building.

# Fellows

December 31, 1946

ELECTED

1912. Addison, William H. F., Medical Laboratories, Univ. of Pa.
1926. Adler, Francis Heed, 313 S. 17th St.
1914. Aiken, Thomas G., Berwyn, Pa.
1936. Aldridge, Fred Cutler, Wayne, Pa.
1936. Alexander, Fay Knight, Fitzgerald Mercy Hospital, Darby, Pa.
1906. Allen, Francis Olcott, Jr., 2216 Walnut St.
1932. Allen, Frederick H., 1711 Fitzwater St.
1935. Alpers, Bernard J., 111 North 49th St.
1905. Anspach, Brooke M., 1827 Spruce St.
1930. Appel, Kenneth E., 111 N. 49th St.
1905. Appleman, Leighton Francis, 308 S. 16th St.
1935. Armitage, George L., 400 E. 13th St., Chester, Pa.
1922. Arnett, John H., 2116 Pine St.
1942. Aronson, Joseph D., Henry Phipps Institute, 7th and Lombard St.
1920. Astley, G. Mason, 812 N. 63rd St.
1944. Atkins, Joseph P., 1201 Knox Rd., Wynnewood, Pa.
1935. Atlee, John L., 37 E. Orange St., Lancaster, Pa.
1935. Atlee, John L., Jr., 37 E. Orange St., Lancaster, Pa.
1914. Austin, J. Harold, 821 Maloney Clinic, Univ. of Pa.
1935. Bach, Theodore F., 1900 Rittenhouse Sq.
1942. Bachman, Carl, Univ. of Pa. Hospital.
1937. Bacon, Emily P.,1930 Chestnut St.
1946. Baker, Walter W., 255 S. 17th St.
1916. Balentine, Percy L., 407 Weightman Bldg., 1524 Chestnut St.
1898. Balliet, Tilghman M., 3920 Sansom St.
1940. Barba, Philip S., 222 W. Harvey St.
1943. Barden, Robert P., 3400 Spruce St.
1911. Barnard, Everett P., 1820 S. Rittenhouse Sq.
1939. Barnshaw, Harold D., 406 Cooper St., Camden, N. J.
1939. Bartle, Harvey Jr., 133 S. 36th St.
1924. Bartle, Henry J., 1930 Chestnut St.
1931. Bates, William, 2029 Pine St.
1932. Batson, Oscar V., 3502 Hamilton St.
1921. Bauer, Edward L., 1609 Spruce St.
1933. Bauer, John T., 312 E. Second St., Moorestown, N. J.
1939. Baumann, Frieda, 1930 Chestnut St.
1922. Bazett, Henry C., Medical School, Univ. of Pa.
1908. Beardsley, E. J. G., 1919 Spruce St.
1930. Beardwood, Joseph T., Jr., 2031 Locust St.
1935. Beerman, Herman, 2422 Pine St.
1932. Behney, Charles A., 3722 Chestnut St.
1942. Behrend, Albert, 255 S. 17th St.
1945. Behrend, Bernard, 5910 Greene St.
1934. Behrend, Moses, 255 S. 17th St.
1930. Belk, William Parks, Times Medical Bldg., Ardmore, Pa.
1936. Bell, Benjamin Tertius, Abington Memorial Hospital, Abington, Pa.

1943. Berk, J. Edward, Medical Tower Bldg.
1941. Bernstein, Mitchell, 1321 Spruce St.
1937. Bertolet, J. Allen, 1530 Locust St.
1934. Biddle, Sydney Geoffrey, 255 S. 17th St.
1918. Billings, Arthur E., 2020 Spruce St.
1917. Birdsall, Joseph C., 139 Booth Lane, Haverford, Pa.
1933. Bishop, Paul A., Pennsylvania Hospital.
1944. Blady, John V., 222 Meeting House La., Merion, Pa.
1917. Block, Frank B., 136 S. 16th St.
1929. Bockus, Henry L., 250 S. 18th St.
1928. Boles, Russell S., Rittenhouse Plaza.
1923. Bond, Earl D., 111 N. 49th St.
1911. Bonney, Charles W., 255 S. 17th St.
1924. Boon, David J., 3131 W. Penn St.
1931. Bortz, Edward Le Roy, 2021 W. Girard Ave.
1921. Borzell, Francis Frank, 4940 Penn St.
1936. Bostwick, Delazon Swift, 106 Linwood Ave., Ardmore, Pa.
1928. Bothe, Albert E., 255 S. 17th St.
1928. Bothe, Frederick A., 255 S. 17th St.
1923. Bower, John O., 2008 Walnut St.
1942. Bowie, Morris A., 910 Old Lancaster Road, Bryn Mawr, Pa.
1907. Boyer, Henry P., 4602 Baltimore Ave.
1925. Boykin, Irvine M., 136 S. 16th St.
1929. Bradbury, Samuel, 151 W. Coulter St.
1907. Bradley, William Nathaniel, 1725 Pine St.
1942. Branen, William, Whitby & Cypress Ave., Yeadon, Pa.
1921. Bransfield, John W., 2101 Spruce St.
1946. Brisco, Clarence Conway, Medical Tower, 255 S. 17th St.
1917. Bromer, Ralph S., 318 Milbank Road, Bryn Mawr, Pa.
1936. Brown, Charles L., 1030 Indian Creek Rd.
1936. Brown, Clark E., Lankenau Hospital.
1932. Brown, Claude P., 1930 Chestnut St.
1919. Brown, Henry P., Jr., 1930 Chestnut St.
1939. Brust, Raymond W., 4710 Chester Ave.
1930. Bucher, Carl Joseph, The Westbury, 15th & Spruce Sts.
1943. Buerki, Robin C., University of Pa.
1928. Burden, Verne G., 255 S. 17th St.
1940. Burnett, W. Emory, 3401 N. Broad St.
1941. Butler, Miriam, 1930 Chestnut St.
1906. Butler, Ralph, 1930 Chestnut St.
1907. Cadwalader, Williams B., 133 S. 36th St.
1928. Campbell, Edward H., Spruce Street Medical Bldg., 19th & Spruce Sts.
1944. Campion, Richard J., Penllyn Rd., Springhouse, Ambler, Pa.
1931. Cantarow, Abraham, 1025 Walnut St.
1935. Carey, Lawrence S., 1930 Chestnut St.
1931. Cariss, Walter L., 2043 Walnut St.
1930. Carpenter, Chapin, 1930 Chestnut St.
1905. Carpenter, Herbert B., 1805 Spruce St.
1926. Carpenter, Howard Childs, 1805 Spruce St.
1917. Carson, John B., 1802 Pine St.
1922. Case, Eugene A., 63 W. La Crosse Ave., Landsdowne, Pa.
1937. Castallo, Mario A., 1621 Spruce St.

1943. Castigliano, S. Gordon, 1012 Hampstead Rd., Penfield Downs, Del. Co., Pa.
1933. Chamberlain, W. Edward, Temple University Hospital.
1939. Chamberlain, George W., Reading Hospital, Reading, Pa.
1900. Chance, Burton, 317 S. 15th St.
1945. Chance, Burton, Jr., 1726 Spruce St.
1939. Charr, Robert Kyun Hyun, 2038 Locust St.
1941. Cheleden, John, 255 S. 17th St.
1945. Cianfrani, Theodore, 1930 Chestnut St.
1939. Ciccone, Emmet F., 2021 Murray St.
1929. Clark, Eliot R., 315 S. 41st St.
1934. Clark, Jefferson Hamer, 3701 N. Broad St.
1926. Clerf, Louis H., 1530 Locust St.
1910. Cloud, J. Howard, 11 W. Montgomery Ave., Ardmore, Pa.
1903. Coates, George Morrison, 1721 Pine St.
1908. Codman, Charles A. E., S.E. Corner 42d and Spruce Sts.
1941. Cohen, J. Gershon, 255 S. 17th St.
1907. Cohen, Myer Solis-, 2110 Spruce St.
1888. Cohen, S. Solis-, Mountain & Cheltenham Aves.
1920. Cole, Charles J., 7926 Park Ave., Elkins Park, Pa.
1934. Colgan, Robert C., Bridgeport, Pa.
1934. Collins, Leon Howard, Jr., 133 S. 36th St.
1943. Colonna, Paul C., Univ. of Pa. Hospital.
1945. Coonel, Pauline, 5908 Greene St.
1930. Cooper, David A., 1520 Spruce St.
1941. Cornelius, Chalmers E., 119 Summit Ave., Jenkintown, Pa.
1911. Cornell, Walter S., Board of Public Education, Parkway and 21st St.
1945. Corrigan, Patrick H., 1720 S. Broad St., Trenton, N. J.
1914. Corson, Edward F., 136 S. 16th St.
1946. Costello, Thomas J., 131 Pennsylvania Avenue, Bryn Mawr, Pa.
1924. Cowan, Alfred, 1930 Chestnut St.
1940. Cowan, Thomas H., 1930 Chestnut St.
1904. Craig, Frank A., The Henry Phipps Institute, 7th and Lombard Sts.
1907. Crampton, George S., 2031 Locust St.
1937. Crane, Martin P., 2412 N. Broad St.
1920. Creighton, William J., 37 S. 20th St.
1941. Creskoff, Adolph J., 3400 Spruce St.
1920. Cross, George H., Chester, Pa.
1917. Cross, Sumner H., P. O. Box 126, Jenkintown, Pa.
1921. Crossan, Edward T., 5324 Wayne Ave.
1940. Crowe, Aldrich C., 735 Atlantic Ave., Ocean City, N. J.
1904. Cruice, John M., 407 S. 22d St.
1937. Crump, Jean, 1930 Chestnut St.
1937. Curtis, Lawrence, 255 S. 17th St.
1934. Custer, R. Philip, 221 Walnut Ave., Wayne, Pa.
1941. *Cuttle, Tracy D.
1938. Dannenberg, Arthur M., 235 S. 15th St.
1919. Davies, John R., Jr., 2 E. Chestnut Ave., Chestnut Hill.
1936. Davis, David M., 255 S. 17th St.
1937. Davis, Perk Lee, 255 S. 17th St.
1916. Davis, Warren Beagle, 135 S. 18th St.
1935. Deaver, J. Montgomery, 1830 Delancey Pl.

*On active service.

1902. Dehoney, Howard, 240 S. 13th St.
1935. Deibert, Irvin Elmer, 538 Cooper St., Camden, N. J.
1924. Deichler, L. Waller, 1930 Chestnut St.
1923. De Long, Perce, 37 S. 20th St.
1928. Dewees, A. Lovett, Times Medical Bldg., Ardmore, Pa.
1924. Dillon, Edward S., 2016 Delancey Pl.
1932. Dintenfass, Henry, 1305 Spruce St.
1920. Diven, John, 1827 Delancey St.
1941. Dixon, Harold M., 36 E. Front St., Media, Pa.
1920. Doane, Joseph C., 617 W. Hortter St.
1946. Donnelly, Andrew J., 4931 State Road, Drexel Hill, Pa.
1942. Donnelly, Edward J., 1321 Spruce St.
1933. Donnelly, Joseph C., 255 S. 17th St.
1937. Donnelly, Robert T. M., 255 S. 17th St.
1907. Dorrance, George M., 2101 Spruce St.
1933. Downs, T. McKean, 921 Mt. Pleasant Rd., Bryn Mawr, Pa.
1910. Drayton, William, Jr., 1930 Spruce St.
1935. Duane, William, Jr., 2100 Walnut St.
1944. Dublin, George J., 1930 Chestnut St.
1944. Dugger, John H., 3902 Vaux St.
1935. Duncan, Garfield G., 330 S. 9th St.
1937. Dunn, Charles W., 269 S. 19th St.
1942. Durant, Thomas M., 3401 N. Broad St.
1942. Dyer, W. Wallace, 2016 Delancey Pl.
1935. Eads, John T., 2029 Delancey St.
1911. Earnshaw, Henry C., Bryn Mawr, Pa.
1936. Easby, Mary Hoskins, 1930 Chestnut St.
1937. Edeiken, Joseph, 1832 Spruce St.
1944. Eger, Sherman A., 2029 Delancey St.
1944. Ehrich, William E., 236 W. Hortter St.
1930. Eiman, John, Cynwyd, Pa.
1946. Elfman, Louis Kenneth, 6330 Lebanon Avenue.
1911. Eliason, Eldridge L., 326 S. 19th St.
1939. Ellis, Van Mashburn, 1530 Locust St.
1928. Ellison, Richard T., 269 S. 19th St.
1936. Ellson, J. Vernon, Glendale Rd. & Chestnut St., Upper Darby, Pa.
1904. Elmer, Walter G., 1801 Pine St.
1937. Elsom, Kendall A., 133 S. 36th St.
1934. Ely, William C., 3912 Chestnut St.
1932. Engel, Gilson G., 255 S. 17th St.
1945. English, O. Spurgeon, 255 S. 17th St.
1942. Erb, William H., 133 S. 36th St.
1893. Eshner, Augustus A., 1019 Spruce St.
1944. Estes, William L., Jr., Bethlehem, Pa.
1946. Farell, David M., 1831 Delancey St.
1922. Farley, David L., 4429 Larchwood Ave.
1903. Farr, Clifford B., Bryn Mawr, Pa.
1945. Farrar, George Elbert, Jr., 425 Tregaron Rd., Bala-Cynwyd, Pa.
1930. Farrell, John T., Jr., 255 S. 17th St.
1935. Ferguson, Lewis Kraeer, 133 S. 36th St.
1936. Fetter, Ferdinand, 322 S. 21st St.
1945. Fetter, John S., 1010 Rhawn St.
1935. Fetter, Theodore R., 255 S. 17th St.

1924. Fewell, Alexander G., 1924 Pine St.
1943. Finkelstein, Arthur, 645 Overhill Rd., Ardmore, Pa.
1945. Fiske, Frederick A., 1530 Locust St.
1928. Fitz-Hugh, Thomas, Jr., 2016 Delancey Pl.
1928. Flick, John B., 330 S. 9th St.
1939. Flippin, Harrison F., 255 S. 17th St.
1946. Forster, Francis M., Jefferson Medical College.
1941. Fox, C. Calvin, 1806 Spruce St.
1906. Fraley, Frederick, 71st and City Line, Overbrook, Pa.
1941. Frazier, William Doane, 133 S. 36th St.
1935. Fridy, Cyrus Ward, 49 E. Levering Mill Rd., Cynwyd, Pa.
1942. Friedman, Reuben, 877 N. 6th St.
1933. Fritch, James Scott, 269 S. 19th St.
1937. Fritz, Herbert H., Pennswood Rd., Bryn Mawr, Pa.
1940. Fry, Kenneth E., 255 S. 17th St.
1935. Fry, Wilfred Eyles, 1819 Chestnut St.
1937. Furlong, Thomas F., Jr., Times Medical Building, Armore, Pa.
1935. Gammon, Geo. D., Univ. of Pa. Hospital.
1931. Garner, Vaughn C., Germantown Professional Building.
1935. Geist, Donald C., 5302 Spruce St.
1917. Gerhard, Arthur H., 1615 N. Delaware Ave.
1899. Gibbon, John H., Media, Pa.
1934. Gibbon, John H., Jr., 4035 Pine St.
1939. Gibson, Glen Gregory, 255 S. 17th St.
1944. Gifford, Edward S., Jr., 1913 Spruce St.
1933. Gifford, U. Grant, Kennett Square, Pa.
1920. Gill, A. Bruce, 1930 Chestnut St.
1927. Gilmour, William R., 413–14 Weightman Bldg., 1524 Chestnut St.
1931. Giordano, Anthony A. S., 1819 S. Broad St.
1906. Gittings, John C., Harwood, Md.
1906. Goepp, R. Max, 1333 Chestnut St.
1945. Goldberg, Samuel J., 1723 Pine St.
1933. Goldburgh, Harold L., 1932 Spruce St.
1935. Goldsmith, N. Ralph, 136 S. 16th St.
1905. Gordon, Alfred, 1520 Spruce St.
1928. Gordon, Burgess L., 1832 Spruce St.
1937. Gordon, William, 1721 Pine St.
1941. Gouterman, Joseph I., 1930 Chestnut St.
1894. Graham, Edwin E., 1713 Spruce St.
1926. Grant, Francis Clark, Univ. of Pa. Hospital.
1933. Greenbaum, Sigmund S., 320 S. 18th St.
1940. Greene, Lloyd B., 136 S. 16th St.
1934. Griffith, John Q., Jr., 133 S. 36th St.
1945. Griffiths, John E., Mermont Apartments, Bryn Mawr, Pa.
1941. Groff, Robert A., 700 University of Pa. Hospital.
1933. Gruber, Charles M., 128 Overhill Rd., Cynwyd, Pa.
1932. Guequierre, Jacques P., Mermont Plaza, Bryn Mawr, Pa.
1944. Gunter, John H., 1306 Knox Rd., Wynnewood, Pa.
1945. György, Paul, Department of Pediatrics, Univ. of Pa.
1935. Hadden, Samuel B., 37 S. 20th St
1945. Hahn, George A., 255 S. 17th St.
1935. Haines, Harlan F., 134 S. State Rd., Upper Darby, Pa.
1939. Hamblock, Leonard C., 255 So. 17th St.

1894. Hamill, S. McC., 1822 Spruce St.
1897. Hand, Alfred, 1724 Pine St.
1938. Hand, John G., 1724 Pine St.
1932. Harris, Stanley E., Lansdowne, Pa.
1929. Harrison, Francis G., 1900 Spruce St.
1933. Harrison, William John, 135 S. 17th St.
1903. Hart, Charles D., 420 W. Mermaid Lane.
1941. Hartley, Harriet L., 1719 Rittenhouse Square.
1932. Hartman, J. Calvin, 50 W. Walnut Lane.
1926. Hartmann, Fred L., 1914 Pine St.
1946. Harvey, Edith E., 1930 Chestnut St.
1935. Haskell, Benjamin F., 1426 Spruce St.
1946. Hatfield, C. Alexander, 2019 Spruce St.
1907. Hatfield, Charles James, Henry Phipps Institute, 7th and Lombard Sts.
1911. Heed, Charles R., 1205 Spruce St.
1946. Hendrickson, Frank O., 37 S. 20th St.
1944. Herbut, Peter A., Jefferson Medical College Hospital.
1927. Herman, Leon, 136 S. 16th St.
1944. Hershey, J. Ivan, 935 Bowman Ave., Wynnewood, Pa.
1924. Hewson, William, 2031 Locust St.
1924. Hirst, John C., 2d, 500 N. 20th St.
1944. Hirst, Otto C., 255 S. 17th St.
1908. Hitchens, Arthur Parker, Dept. Public Health, Wilmington, Del.
1943. Hitschler, William J., 8840 Germantown Ave.
1944. Hneleski, Ignatius S., 802 S. 48th St.
1943. Hockaday, Agnes, 316 Shadeland Ave., Drexel Hill, Pa.
1939. Hodes, Philip J., Univ. of Pa. Hospital.
1931. Holland, H. Albert, 8200 Crittenden St., Chestnut Hill.
1933. Hollingshead, Irving W., 123 S. 18th St.
1932. Hollingsworth, I. Pemberton P., 411 N. Walnut St., West Chester, Pa.
1919. Hopkins, Arthur H., 1726 Pine St.
1925. Hopkinson, R. Dale, Jenkintown, Pa.
1946. Horan, Gerald W., 5819 Chester Ave.
1944. Housel, Edmund L., 255 S. 17th St.
1928. Houser, Karl Musser, 2010 Spruce St.
1938. Howell, John Carnett, 326 S. 19th St.
1946. Howson, John Yeatts, 3722 Chestnut St.
1937. Hughes, Joseph, 111 N. 49th St.
1939. Hughes, P. Boland, 419 Hillbrook Rd., Bryn Mawr, Pa.
1923. Hume, John E., 37 S. 20th St.
1946. Hunt, William T., Jr., 1205 Spruce St.
1921. Hunter, Robert John, 2035 Delancey Pl.
1926. Husik, David N., 1820 Spruce St.
1934. Hustead, Frank H., 5112 N. Broad St.
1935. Ingleby, Helen, Jewish Hospital, York & Tabor Rds.
1921. Ivy, Robert H., 1930 Chestnut St.
1917. Jackson, Chevalier, 255 S. 17th St.
1932. Jackson, Chevalier L., 255 S. 17th St.
1934. Jacobs, Maurice, 1831 Delancey Place.
1941. Jeffers, William A., University of Pa. Hospital.
1928. John, Rutherford L., 256 S. 21 St.
1942. Johnson, Julian, 406 Conshohocken State Rd., Narberth, Pa.
1938. Johnson, Thomas A., 250 S. 18th St.

1918. Jonas, Leon, 255 S. 17th St.
1943. *Jones, Charles Alexander.
1924. Jones, Harold W., 1930 Chestnut St.
1900. Judson, Charles F., 252 Kent Road, Wynnewood, Pa.
1902. Jump, Henry Draper, 1530 Locust St.
1936. Kain, Thomas M., 403 Cooper St., Camden, N. J.
1938. Kasper, Kelvin A., 135 S. 18th St.
1945. Katz, G. Henry, 111 N. 49th St.
1941. Kauffman, M. Luther, Medical Arts Bldg., Jenkintown, Pa
1938. Keeler, Harold R., 136 S. 16th St.
1935. Kelley, George F. J., N.E. Cor. 20th and Chestnut Sts.
1932. Kelly, Herbert T., 1900 Spruce St.
1912. Kelly, Thomas C., 105 School Lane.
1941. Kennedy, Patrick J., 6910 Market St., Upper Darby, Pa.
1921. Kern, Richard A., University of Pa. Hospital.
1935. Keyes, Baldwin L., 2031 Locust St.
1930. Kimbrough, Robert A., Jr., 807 Spruce St.
1936. King, Orville C., 330 S. 9th St.
1920. Klauder, Joseph V., 1934 Spruce St.
1920. Klein, Thomas, 250 S. 18th St.
1934. Kline, Oram R., 414 Cooper St., Camden, N. J.
1932. Klopp, John W., 600 W. Olney Ave.
1943. Kneedler, William H., 8801 Crefeld St.
1919. Knipe, Norman L., 1930 Chestnut St.
1908. Knowles, Frank C., 2035 Spruce St.
1938. Knox, Andrew, 1930 Chestnut St.
1925. Knox, Harry E., 719 66th Ave.
1945. Kobler, H. B., 658 N. 63rd St.
1914. Kolmer, John A., Cynwyd, Pa.
1936. Konzelmann, Frank Williamson, 304 Shore Rd., Absecon, N. J.
1941. Krall, J. Thomas, 1927 Spruce St.
1944. Krauss, Frederick Harold, 1930 Chestnut St.
1941. Krewson, William E., 3rd, 1930 Chestnut St.
1914. Krumbhaar, Edward B., School of Medicine, Univ. of Pa.
1944. LaMotte, William O., Medical Arts Bldg., Wilmington, Del.
1946. Lampe, William T., 4207 Tyson Ave.
1907. Langdon, H. Maxwell, 1530 Locust St.
1933. Langdon, Roy L., 5917 Greene St., Germantown.
1941. Langner, Paul H., Jr., 130 S. 18th St.
1945. Lansbury, John, 3401 N. Broad St.
1934. Laplace, Louis B., 200 Glenn Rd., Ardmore, Pa.
1926. Laws, George M., 1907 Spruce St.
1936. Leaman, William G., Jr., 3700 Baring St.
1920. Leavitt, Frederic Headley, 1527 Pine St.
1941. Leberman, Paul R., 136 S. 16th St.
1934. Lee, Thomas B., 622 Cooper St., Camden, N. J.
1908. Lee, Walter Estell, 1833 Pine St.
1942. Lehman, James A., 255 S. 17th St.
1936. Lehrfeld, Louis, 1321 Spruce St.
1944. Lell, William A., 203 W. Chestnut Ave.
1935. Lemmon, William T., 1930 Chestnut St.

* On active service.

1943. Leopold, Irving H., 1930 Chestnut St.
1920. Leopold, Simon S., 2025 Spruce St.
1944. Lettiere, Anthony J., 425 E. State St., Trenton, N. J.
1933. Levering, J. Walter, Abington Memorial Hospital, Abington, Pa.
1915. Lewis, Fielding O., Providence Road, Media, Pa.
1938. Lewis, James P., 3815 Chestnut St.
1936. Lillie, Walter I., 255 S. 17th St.
1940. Limberger, William A., 301 S. Church St., West Chester, Pa.
1938. Lindauer, M. August, 133 S. 36th St.
1927. Lindsey, Walter H., 810 W. Dauphin St.
1936. Lintgen, Charles, 1930 Chestnut St.
1945. Lisker, Samuel, 1930 Chestnut St.
1944. Livezey, Mary M., 7200 Cresheim Rd.
1936. Llewellyn, Thomas H., 910 N. 63rd St.
1907. Lodholz, Edward, 431 S. 45th St.
1931. Loewenberg, Samuel A., 1905 Spruce St.
1938. Long, Charles-Francis, 1836 Delancey Pl.
1933. Long, Esmond R., Henry Phipps Institute, 7th and Lombard Sts.
1935. Long, William L., 2025 Walnut St.
1893. Longaker, Daniel, 5702 Overbrook Ave.
1931. Longaker, Edwin P., 41 E. Montgomery Ave., Ardmore, Pa.
1944. Loudenslager, Paul E., 2101 Spruce St.
1942. Lownes, John B., 136 S. 16th St.
1936. Lucchesi, Pascal Francis, Philadelphia General Hospital.
1921. Lucké, Balduin H. E., School of Medicine, Univ. of Pa.
1932. Lukens, Francis D. W., Univ. of Pa. Hospital.
1938. Lukens, Philip Jefferson, 158 E. Butler Ave., Ambler, Pa.
1930. Lukens, Robert M., Medical Arts Bldg., 16th and Walnut Sts.
1929. Lull, Clifford B., Women's Bldg., Penna. Hosp., 807 Spruce St.
1939. Luongo, Romeo A., 2054 Locust St.
1919. Lynch, Frank B., Jr., Germantown Hosp., Penn and Chew Sts.
1914. Lyon, B. B. Vincent, Box 955, Winter Park, Fla.
1933. McAndrews, Leo F., Mermont Plaza, Bryn Mawr, Pa.
1932. McCahey, James F., 1534 Pine St.
1900. McCarthy, Daniel J., 2025 Walnut St.
1936. McCarthy, Patrick A., Central Medical Bldg.
1935. McClenahan, William U., 5 E. Chestnut Ave.
1931. McCloskey, Edward, 7 E. Chestnut Ave.
1942. McCloskey, John F., 8720 Germantown Ave.
1935. McConnell, James W., 20th and Chestnut Sts.
1934. McCouch, Grayson P., Medical School, Univ. of Pa.
1938. McCrea, Lowrain E., 1930 Chestnut St.
1937. McCutcheon, Morton, Alden Park Manor.
1942. McDonald, P. Robb, 255 S. 17th St.
1945. McGee, Lemuel Clyde, Hercules Powder Company, Wilmington, Del.
1937. McGuinness, Aims C., 8614 Montgomery Ave.
1940. McLaughlin, Edward F., 4116 N. Broad St.
1933. McLaughlin, James S., 330 S. 9th St.
1924. McMillan, Thomas M., 2044 Locust St.
1924. McPhedran, F. Maurice, Germantown Hosp., Penn and Chew Sts.
1943. Macfarlan, Douglas, 1805 Chestnut St.

* On active service.

1932. Macfarlane, Catharine, 136 S. 16 St.
1939. Macneill, Norman N., 5807 Chew St.
1935. Maeder, LeRoy M. A., 206 S. 13th St.
1935. Maier, Ernest G., 1323 N. 15th St.
1942. Manges, Lewis C., Jr., 319 S. 16th St.
1936. Mann, Bernard, 2019 Pine St.
1937. Margolies, Alexander, 1836 Delancey Pl.
1941. Martin, James R., 136 S. 16 St.
1935. Matthews, Robert A., 111 N. 49th St.
1939. May, Hans, 255 S. 17th St.
1934. *Mecray, Paul M.
1914. Mencke, J. Bernhard, 1816 Spruce St.
1941. Mendell, Theodore H., 2023 Spruce St.
1943. Meranze, David R., 1031 Lakeside Ave.
1937. Meyer, George Phillip, 410 Haddon Ave., Camden, N. J.
1935. Miller, Ford A., 4016 Chestnut St.
1946. Miller, Franklin R., Jefferson Medical College.
1934. Miller, Hugh McCauley, 1614 Locust St.
1939. Miller, Malcolm W., 255 S. 17th St.
1939. Miller, Merle M., 6013 Greene St.
1932. Miller, M. Valentine, 114 W. Phil-Ellena St.
1921. Miller, T. Grier, Univ. of Pa. Hospital.
1937. Missett, Joseph Vincent, Jr., 1814 Spruce St.
1904. Mitchell, Charles Franklin, 2003 Pine St.
1932. Mohler, Roy W., 1806 Spruce St.
1936. Montgomery, Hugh, 119 Glenn Road, Ardmore, Pa.
1936. Montgomery, John B., 1930 Chestnut St.
1932. Montgomery, Thaddeus L., 2031 Locust St.
1928. Moon, Virgil H., Jefferson Medical College.
1935. Moore, John Royal, Beury Bldg., Broad St. and Erie Ave.
1924. Moorhead, Stirling W., 1523 Pine St.
1936. Morgan, David R., Jefferson Medical College.
1893. Morris, Elliston J., 439 Midland Ave., St. Davids, Del. Co., Pa.
1944. Morris, Harold H., Villa Nova, Pa.
1945. Morris, I. Paul, 255 S. 17th St.
1941. Muckle, Craig Wright, 255 S. 17th St.
1929. Mudd, Stuart, Department of Bacteriology, Medical School, Univ. of Pa.
1935. Mullen, Carroll Richard, 2025 Locust St.
1934. *Mullen, Edward A.
1905. Muller, George P., 326 S. 19th St.
1930. Murphy, Douglas P., University Hospital.
1934. Murphy, Eugene C., 1841 S. Broad St.
1905. Mutschler, Louis H., 1625 Spruce St.
1945. Naide, Meyer, 2034 Spruce St.
1936. Nelson, Guy M., 255 S. 17th St.
1943. Nelson, Waldo E., 615 Moreno Rd., Narberth, Pa.
1905. Newcomet, William S., 3501 Baring St.
1938. Newton, Zachariah B., 601 E. Sedgwick St.
1935. Nicholson, Jesse Thompson, Pennsylvania Hospital.
1899. Nicholson, William Rufus, 1930 Chestnut St.
1941. Nisbet, Verner, 254 S. 45th St.

* On active service.

1905. Norris, Charles C., Darby and Goshen Roads, Bryn Mawr, Pa.
1938. Norris, Robert F., 905 Pine St.
1941. Odenatt, Wm. Burrill, 1213 W. Lehigh Ave.
1913. O'Neal, Alexander Hay, St. Davids, Pa.
1936. Orr, Theodore E., 1930 Chestnut St.
1913. Outerbridge, George W., 1927 Spruce St.
1915. Owen, Hubley R., 319 S. 16th St.
1897. Packard, Francis R., 304 S. 19th St.
1909. Parish, Benjamin Dores, 1927 Spruce St.
1945. *Park, Felix Roman.
1940. Parker, Alan P., 330 S. 9th St.
1944. Paschkis, Karl E., Jefferson Medical College.
1931. Paul, John Davis, 3112 N. Broad St.
1932. Payne, Franklin L., Univ. of Pa. Hospital.
1943. Pearson, Gerald H., 111 N. 49th St.
1922. Pelouze, P. S., 1216 Drexel Ave., Drexel Hill, Pa.
1909. Pemberton, Ralph, Paoli, Pa.
1930. Pendergrass, Eugene P., Univ. of Pa. Hospital.
1932. Pennell, Howard Y., West Chester, Pa.
1944. Pennypacker, Charles S., 111 E. Montgomery Ave., Ardmore, Pa.
1939. Pepper, D. Sergeant, 122 Grays Lane, Haverford, Pa.
1914. Pepper, O. H. Perry, Univ. of Pa. Hospital.
1902. Pepper, William, 1112 Prospect Ave., Melrose Park, Pa.
1916. Percival, Milton Fraser, 2332 S. Broad St.
1942. Perkins, William Harvey, 1025 Walnut St.
1946. Perloff, William Harry, 2106 Spruce St.
1940. Pessel, Johannes F., 224 West State St., Trenton, N. J.
1937. Pettit, Horace, P.O. Box 96, Gladwyne, Pa.
1905. Pfahler, George E., 1930 Chestnut St.
1915. Pfeiffer, Damon B., Meadowbrook, Pa.
1946. Pfeiffer, Mildred C. J., 331 S. Smedley St.
1935. Phillips, Arthur W., 3904 Walnut St.
1911. Piersol, George Morris, Univ. of Pa. Hospital.
1933. Pillsbury, Donald M., 133 S. 36th St.
1922. Pleasants, Henry, Jr., West Chester, Pa.
1937. Polk, David Stewart, Rosemont, Pa.
1932. Porter, Roland De Lance, Jenkintown, Pa.
1931. Pryor, Charles Allen, 255 S. 17th St.
1943. Radbill, Samuel X., 7043 Elmwood Ave.
1945. Rakoff, Abraham Edward, 2001 Delancey Pl.
1931. Ramsey, Frank M., Chestnut Hill.
1913. Randall, Alexander, 136 S. 16 Street.
1941. Rankin, Charles A., Ludlow & Heather Rd., Upper Darby, Pa.
1946. Rapoport, Milton, Children's Hospital, 1740 Bainbridge St.
1926. Ravdin, I. S., Univ. of Pa. Hospital.
1938. Read, Hilton Shreve, 5407 Atlantic Ave., Atlantic City, N. J.
1928. Reese, Warren S., 1901 Walnut St.
1925. Reeves, Rufus S., 2227 Spruce St.
1920. Rehfuss, Martin E., 131 St. George's Rd., Ardmore, Pa.
1921. Reiff, E. Paul, 1927 Spruce St.
1937. Reimann, Hobert A., Jefferson Hospital.

* On active service.

1919. Reimann, Stanley P., 703 W. Phil-Ellena St.
1923. Repplier, Sidney J., 373 Roumfort Rd., Mt. Airy.
1945. Rhoads, Jonathan E., University Hospital.
1936. Richards, James L., Haverford Villa, Ardmore, Pa.
1919. Richardson, Russell, 320 S. 16th St.
1919. Ridpath, Robert F., 1737 Chestnut St.
1942. Riggs, Helena E., Philadelphia General Hospital.
1936. Ritter, Joseph A., 2405 N. 54th St.
1933. de Rivas, Damaso, 1831 Chestnut St.
1942. Rivers, Thurston D., 111 N. 49th St.
1932. Robbins, Frederick R., 317 Millbank Rd., Bryn Mawr, Pa.
1939. Roberts, Ella, 133 S. 36th St.
1944. Roberts, Joseph E., 403 Cooper St., Camden, N. J.
1899. Roberts, Walter, 1921 Spruce St.
1932. Robertson, Harold F., 327 S. 17th St.
1903. Robertson, William Egbert, 327 S. 17th St.
1938. Roche, Philip Q., 255 S. 17th St.
1912. Rodman, John Stewart, 1726 Spruce St.
1934. Rogers, Harry L., Riverton, N. J.
1928. Rose, Edward, 426 Owen Rd., Wynnewood, Pa.
1936. Rose, Elizabeth Kirk, 426 Owen Rd., Wynnewood, Pa.
1946. Rosemond, George Parrott, Temple University, Broad & Ontario Sts.
1932. Rothrock, Harry A., West Chester, Pa.
1936. Rothschild, Norman, 245 S. 16th St.
1933. Rowntree, Leonard George, 1520 Spruce St.
1937. Roxby, John B., R.D. 1, Souderton, Pa.
1941. Royster, Hubert A., Jr., The Mermont, Bryn Mawr, Pa.
1933. Rudolphy, Jay Besson, 230 S. 21st St.
1946. Rupp, Charles, 2315 Delancey Pl.
1945. Rynes, Samuel E., 334 S. 21st St.
1944. Sampson, David Alan, 726 Braeburn Lane, Penn Valley, Narberth, Pa.
1936. Sands, Joseph Evans, Rosemont, Pa.
1908. Sautter, Albert C., Germontown Professional Bldg.
1920. Scarlett, Hunter W., 230 S. 21st St.
1939. Scattergood, Joseph Jr., 115 S. High St., West Chester, Pa.
1917. Schaeffer, J. Parsons, Daniel Baugh Institute, 307 S. 11th St.
1929. Scheffey, Lewis C., 255 S. 17th St.
1942. Scheie, Harold G., 313 S. 17th St.
1945. Schell, James F., Veterans Hospital, New Castle, Del.
1929. Schenck, Harry P., 1235 Wyngate Rd., Wynnewood, Pa.
1945. Schlezinger, Nathan S., Medical Tower Building.
1917. Schnabel, Truman G., 1704 Pine St.
1917. Schoff, Charles H. Media, Pa.
1928. Schofield, Frederick S., 5501 Greene St.
1921. Schumann, Edward A., 1814 Spruce St.
1930. Scott, John Porter, 1740 Bainbridge St.
1940. Scott, T. F. McNair, Children's Hospital, 1740 Bainbridge St.
1924. Shallow, Thomas A., 1611 Spruce St.
1908. Shannon, Charles E. G., 1930 Chestnut St.
1928. Sharpless, Frederick C., Rosemont, Pa.
1897. Sharpless, William T., West Chester, Pa.
1931. Sheehan, William C., 8811 Germantown, Ave.

1946. Shepherd, Samuel Garfield, 2039 Pine St.
1932. Sheridan, Joyce T., 412 W. Durham St.
1943. Shewbrooks, Daniel M., Penn Mutual Life Ins. Co., 6th and Walnut Sts.
1936. Shipman, James Shelby, 255 S. 17th St.
1935. Shoemaker, Robert, 3rd., 68 Byberry Rd., Hatboro, Pa.
1946. Shoup, George Daniel, 7007 N. 12th St.
1939. *Shumway, Norman P.
1936. Shuster, Benjamin H., 1824 Pine St.
1941. Silcox, Louis E., 255 S. 17th St.
1903. Sinclair, John F., 4103 Walnut St.
1907. Sinkler, Francis W., P.O. Box 373, Bryn Mawr, Pa.
1928. Skillern, Samuel R., 1734 Pine St.
1933. Smelzer, Donald Campbell, Germantown Hosp., Penn and Chew Sts.
1929. Smith, Austin T., 1830 Spruce St.
1933. Smith, Lauren Howe, 111 N. 49th St.
1927. Smyth, Calvin Mason, Room 451, Methodist Hospital, Broad and Wolf Sts.
1938. Snodgrass, L. E., 2011 Chestnut St.
1941. Snyder, G. Gordon, Mermont Apts., Bryn Mawr, Pa.
1935. Sokoloff, Martin J., 255 S. 17th St.
1940. Soloff, Louis A., 2032 Pine St.
1935. Sommer, George N. J., 120 W. State St., Trenton, N. J.
1944. Sommer, George N. J., Jr., 120 W. State St. Trenton, N. J.
1928. Spaeth, Edmund B., 1930 Chestnut St.
1937. Spangler, John Luther, Devon, Pa.
1935. Spiegel, Ernest, 6807 Lawnton Ave., Oak Lane.
1929. Sponsler, Marshall B., 1737 Chestnut St.
1944. Stadie, William C., University Hospital.
1927. Starr, Isaac, 505 Cresheim Valley Rd.
1945. Stecher, H. Armin, 1510 Darby Rd., Upper Darby, Pa.
1946. Stein, Irvin, 269 South 19th St.
1936. Steinfield, Edward, N.E., Cor. 18th and Chestnut Sts.
1942. Stengel, Alfred, Jr., Lancaster Ave. and Cambria Court, St. Davids, Pa.
1914. Stewart, Thomas S., The Barclay, 18th and Rittenhouse Sq.
1941. Stewart, Winifred B., 1930 Spruce St.
1934. Stimson, Cheney M., 167 Harvey St.
1925. Stokes, John H., 4228 Spruce St.
1928. Stokes, Joseph, Jr., 1740 Bainbridge St.
1943. Stokes, S. Emlen, 129 Chester Ave., Moorestown, N. J.
1923. Strecker, Edward A., 111 N. 49th St.
1923. Stroud, William Daniel, 1011 Clinton St.
1937. Strumia, Max M., Penn Valley, Narberth, Pa.
1933. Stuckert, Harry, 248 S. 21st St.
1937. Sturgis, Margaret C., 2305 Arendell St., Morehead City, N. C.
1927. Sturgis, Samuel Booth, 2305 Arendell St., Morehead City, N. C.
1934. Summey, Thomas J., 330 S. 9th St.
1930. Sunderman, F. William, 2210 Delancey Pl.
1936. Surver, James Miller, 1832 Spruce St.
1928. Swartley, William B., 6002 Greene St.
1934. Sweeney, John A., 1900 Rittenhouse Sq.
1944. Swenson, Paul C., Jefferson Hospital.
1943. Tassman, Isaac S., 136 S. 16th St.

* On active service.

1946. Tauber, Robert, 2019 Walnut St.
1933. Taylor, Herbert W., Haverford, Pa.
1931. Taylor, Norman H., 100 W. Evergreen Ave.
1946. Thomas, Carmen C., 1930 Chestnut St.
1928. Thomas, J. Earl, Drexel Hill, Pa.
1907. Thomas, T. Turner, 1636 Francis St.
1942. Thompson, Wesley, D. Jr., 18 N. Main St. Lewistown, Pa.
1927. Thorington, J. Monroe, 2031 Chestnut St.
1936. Thorton, Mary Bickings-, 2703 West Somerset St.
1936. Thorp, Francis Quicksall, 4900 Penn St.
1936. Thudium, William J., 136 S. 16th St.
1935. Tocantins, Leandro Maués, 424 W. Hortter St.
1945. Toland, Joseph J., Jr., 1241 W. Lehigh Ave.
1935. Toland, Owen J., Episcopal Hospital, Front and Lehigh Ave.
1945. Tourish, William J., 1832 W. Venango St.
1936. Towson, Charles Emory, Germantown Professional Bldg.
1908. Tracy, Stephen E., 611 Upland Ave., Noble, Pa.
1926. Tucker, Gabriel, 250 S. 18th St.
1938. Tuft, Louis, 1530 Locust St.
1933. Tumen, Henry J., 1900 Rittenhouse Sq.
1938. Turman, Christopher M., Wyncote, Pa.
1923. Turner, Creighton H., 1731 Pine St.
1945. Twyeffort, Louis H., 111 N. 49th St.
1929. Tyson, Ralph M., 255 S. 17th St.
1937. Uhle, Charles A. W., 255 S. 17th St.
1907. Ullom, Josephus T., Carpenter and Quincy Sts.
1937. Vander Veer, Joseph B., 330 S. 9th St.
1937. Van Loon, Emily Lois, 1930 Chestnut St.
1933. Vastine, Jacob H. 2nd, 136 S. 16th St.
1912. Vaux, Norris Wistar, 807 Spruce St.
1940. Voegelin, Adrian W., Germantown Professional Bldg.
1941. *Vogel, Stoughton R.
1903. Wadsworth, William S., 3914 Baltimore Ave.
1927. Wagers, Arthur J., 1429 Spruce St.
1928. Wagoner, George W., Haverford Gables, Haverford, Pa.
1938. Waldman, Joseph, 216 E. Gorgas Lane.
1906. Walker, John K., Media, Pa.
1907. Walker, Warren, 136 S. 16th St.
1932. Walkling, Adolph A., 136 S. 16th St.
1895. Watson, Arthur W., 2013 Locust St.
1932. Watt, Charles C., Jr., 100 W. Coulter St.
1933. Waygood, James Jamison, 3464 School Lane.
1941. Weaver, Ruth H., 2601 Parkway.
1930. Weeder, S. Dana, 250 W. Tulpehocken St.
1920. Weidman, Fred D., 20 Tenby Rd., Havertown, Pa.
1933. Weiss, Benjamin P., The Lenox, 13th and Spruce Sts.
1923. Weiss, Edward, 269 S. 19th St.
1935. Whelan, G. L., 2100 Walnut St.
1921. Whitaker, William, 6771 Germantown Ave.
1936. White, Ellen Pawling Corson-, 1820 Pine St.
1925. Widmann, Bernard P., 250 S. 18th St.

* On active service.

1936. Wilder, Theodore S., Germantown Professional Bldg., Greene and Coulter Sts.
1914. Willard, De Forest P., 1726 Spruce St.
1935. Willard, John Harrington, 334 S. 15th St.
1939. Willauer, George, 6129 Greene St.
1907. Williams, Carl, School Lane and Greene St.
1924. Williams, Horace James, 5908 Greene St.
1937. Williams, John C., 6370 Germantown Ave.
1920. Williams, Philip F., 2206 Locust St.
1927. Williamson, Ernest G., 6353 Woodbine Ave.
1921. Wilson, George, 133 S. 36th St.
1945. Wilson, John F., 1930 Chestnut St.
1942. Wilson, Lucius R., 1305 Morris Road, Wynnewood, Pa.
1937. Wilson, Ross B., 1820 S. Rittenhouse Sq.
1902. Wilson, Samuel M., 1930 Chestnut St.
1940. *Winchell, A. Vaughn.
1941. Wirts, C. Wilmer, 2017 Delancey Pl.
1904. Wister, James W., 5430 Germantown Ave.
1933. Wohl, Michael G., 1727 Pine St.
1944. Wolf, Lewis R., 3474 Frankford Ave.
1918. Wolferth, Charles C., S.E. Cor. 36th & Spruce Sts.
1942. Wolman, Irving J., Lakeside Apts.
1893. Wood, Alfred C., 2035 Walnut St.
1932. Wood, Francis C., 212 Laurel Lane, Haverford, Pa.
1900. Wood, George B., N.E. Corner 20h and Chestnut Sts.
1903. Wood, Horatio C., 319 S. 41st St.
1944. Wood, H. Curtis, Jr., Skippack Pk., Whitemarsh, Pa.
1897. Woodward, George, W. Willow Grove Ave.
1928. Wright, Carroll, S., 1402 Spruce St.
1937. Yaskin, Joseph C., 1832 Spruce St.
1943. Yawger, Nathaniel S., 1524 Chestnut St.
1941. Young, Barton R., Temple University Hosp.
1946. Zeigerman, Joseph H., 1930 Chestnut St.
1894. Zentmayer, William, 1930 Chestnut St.
1933. Zulick, J. Donald, Abington Memorial Hospital, Abington, Pa.

# Non-Resident Fellows

ELECTED

1941. Aronson, Roland S., Fort Sam Houston, Texas.
1934. Bank, Joseph, Phoenix, Arizona.
1903. Biggs, M. H., Rutherfordton, N. C.
1937. Braceland, Francis, J., % Mayo Clinic, 102–11 Second Ave., S.W., Rochester, Minn.
1908. Cadbury, William W., Lingnan University, Canton, China.
1936. Camero, Anthony R., 657 S. Westlake Ave., Los Angeles, Cal.
1936. Clarke, Francis Mann, 116 New St., New Brunswick, N. J.
1930. Cottrell, James E., Memphis, Tennessee.
1942. Craighill, Margaret D., Topeka, Kansas.
1897. Dorland, W. A. Newman, 1236 N. Dearborn Parkway, Chicago, Ill.
1905. Evans, Joseph S., Jr., 1300 University Ave., Madison, Wis.
1940. Forrester, James S., Harrisburg, Pa.
1933. Fowler, Kenneth, 2535 Horton Ave., San Diego, Cal.

* On active service.

1935. Fretz, John Edgar, "Hillcrest" College Hill, Easton, Pa.
1913. Gates, Nathaniel, 10 Peterboro, Detroit, Mich.
1931. Gilman, Robert Louis, Cheyney, Pa.
1936. Guthrie, Donald, 118 S. Wilbur Ave., Sayre, Pa.
1902. Gwyn, Norman B., 109 Madison Ave., Toronto, Canada.
1936. Hatch, Lerleen Clement, 245 Melbourne Ave., Akron, Ohio.
1928. Hayman, Joseph Marchant, Jr., Lakeside Hosp., 2065 Adelbert Rd., Cleveland, Ohio.
1892. Hinsdale, Guy, 1401 Rugby Rd., Charlottesville, Va.
1933. Hitzrot, Lewis H., Medical Director, Mercersburg Academy, Mercersburg, Pa.
1936. Hughes, Brady A., 5005 42d Place, North, Birmingham, Ala.
1899. Jopson, John H., Pawley's Island, S. C.
1931. Kinney, Willard H., 7300 Atlantic Ave., Ventnor, N. J.
1941. Lockwood, John S., Hamden, Conn.
1935. McGuire, Hunter H., 105 N. Braddock St., Winchester, Va.
1900. McReynolds, Robert Phillips, 213 S. Broadway, Los Angeles, Cal.
1935. Mason, James B., Veterans Administration, Washington, D. C.
1932. Meade, Richard H., Jr., Chicago, Illinois.
1936. Middleton, William Shainline, 2114 Adams St., Madison, Wisconsin.
1915. Musser, John H., 1430 Tulane Ave., New Orleans, La.
1937. Nicholson, Samuel T., 2d, The Hill School, Pottstown, Pa.
1905. Norris, George W., Dimock, Pa.
1926. Paul, John Rodman, Dept. Internal Medicine, Yale University, New Haven, Conn.
1907. Price, George E., Stimson Bldg., Seattle, Wash.
1936. Reisinger, John A., 901 20th St., N.W., Washington, D. C.
1907. Royer, B. Franklin, The Hall, R.D. 7, Chambersburg, Pa.
1913. de Schweinitz, George L., 85 E. Broad St., Bethlehem, Pa.
1941. Shands, Alfred R., Jr., Alfred I. duPont Institute, Rockland Rd., Wilmington, Del.
1932. Siegel, Alvin Erdreich, Medical Arts Building, Macon, Ga.
1934. Stewart, Sloan G., Pacific and North Carolina Avenues, Atlantic City, N. J.
1931. Stiles, Merritt H., Spokane, Washington.
1900. Swan, John M., 457 Park Ave., Rochester, N. Y.
1930. Thorpe, Edward S., Jr., Medical Director, St. Paul's School, Concord, N. H.
1941. Tompkins, Pendleton, San Francisco, California.
1913. Vail, William Penn, Blairstown, N. J.
1897. Veasey, Clarence Archiblad, 1569 Paulsen Medical and Dental Bldg., Spokane, Washington.
1931. Walker, Herschel Carey, 320 Park Ave., New York City, N. Y.
1903. Weber, Charles H., 3 Arch Bay, Laguna Beach, California.

# Honorary Fellows

Limited to Fifty, of Whom Twenty May be Foreigners

American

ELECTED

1917. Miner, Charles Howard, B.S., M.D., Member of Board of Directors, Wilkes-Barre General Hospital; Board of Health, Wilkes-Barre; Board of Directors, White Haven Sanitarium Association and Penna. Tuberculosis Society. 264 S. Franklin St., Wilkes-Barre, Pa.
1936. Richards, Alfred Newton, PH.D., SC.D., M.D. (HON.), L.L.D., Professor of Pharmacology, School of Medicine, Vice-president in charge of Medical Affairs, Univ. of Pa. School of Medicine, Univ. of Pa., Phila.
1942. Russell, Frederick Fuller, M.D., Brig. Gen. Med. Corps, U. S. A. (Ret.). Harvard Medical School, Boston, Mass.

### Foreign

1937. Dale, Sir Henry Hallett, c.b.e., f.r.s., m.a., m.d., f.r.c.p., Director, National Institute for Medical Research, Hampstead, Eng. Mt. Vernon House, N.W. 3, Hampstead, London.

1924. Hopkins, Sir F. Gowland, m.d., Biochemical Department, University of Cambridge, Cambridge, England.

1922. McCarrison, Sir Robert, k.t., c.i.e., m.d., d.sc., ll.d., f.r.c.p., Major-General, Indian Medical Service (retired). 18 Linton Rd., Oxford, England.

### Honorary Associates

1942. Conklin, Professor Edwin G., Princeton University, Princeton, N. J.

1942. Donner, William Henry, Lincoln-Liberty Bldg., Philadelphia, Pa.

# Necrological List

| *Resident Fellows* | *Date of Election* | *Date of Death* |
|---|---|---|
| Charles C. A. Banes | March 6, 1940 | August 9, 1946 |
| John T. Carpenter | April 3, 1895 | September 16, 1946 |
| Daniel Louis Dozzi | April 4, 1945 | May 18, 1946 |
| William Evans | April 5, 1905 | March 18, 1945 |
| William J. MacMurtrie | May 11, 1936 | March 22, 1946 |
| F. Hurst Maier | January 7, 1914 | November 1, 1946 |
| Marion Hague Rea | January 6, 1941 | November 1, 1946 |
| Robert P. Regester | January 13, 1931 | June 8, 1946 |
| John Semple Sharpe | May 7, 1928 | May 3, 1946 |
| Richard Manges Smith | January 6, 1936 | December 20, 1946 |
| Joseph Walsh | June 1, 1904 | October 22, 1946 |
| *Non-resident Fellow* | *Date of Election* | *Date of Death* |
| Mazyck P. Ravenel | February 3, 1904 | January 14, 1946 |
| *Foreign Associate Fellow* | *Date of Election* | *Date of Death* |
| Edward Archibald | Elected 1928 | December 17, 1945 |

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1946

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## *of the*

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Printed in U. S. A.

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1946

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Eugene P. Pendergrass

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*Curator of the Mütter Museum and Custodian of the College Collections*

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*Honorary Director of the Department of Medical Arts*

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*Editor of the Transactions & Studies*

W. B. McDaniel, 2d

† Died 18 February 1947.

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